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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex Parte Foster
Appeal No. _____

Applicant:	Michael B. Foster
Serial Number:	09/838,968
Filed:	April 20, 2001
Confirmation No.:	1662
Art Unit:	1653
Examiner:	Kam, Chih Min
Title:	**METHOD OF OPTIMIZING GROWTH HORMONE REPLACEMENT**
Attorney Ref. No.:	RENAS-03

Cincinnati, Ohio November 18, 2003

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF (PATENT APPLICATION-37 CFR 191)

1. Transmitted herewith in triplicate is the APPEAL BRIEF in this application with respect to the Notice of Appeal filed on September 19, 2003.

2. STATUS OF APPLICANT

[ ] other than a small entity

[X] small entity

VERIFIED STATEMENT:

[ ] attached

[X] already filed

3. FEE FOR FILING APPEAL BRIEF

Pursuant to 37 CFR 1.17(f) the fee for filing the Appeal Brief is:

[X] small entity	$165.00
[ ] other than small entity	$330.00

Appeal Brief fee due **$165.00**

4. EXTENSION OF TIME

Applicant petitions for an extension of time under 37 CFR 1.136 for the total number of months checked below:

	Fee for Extension of:	other than small entity	Fee for small entity
___	one month	$ 110.00	$ 55.00
___	two months	$ 420.00	$210.00
___	three months	$ 950.00	$475.00
___	four months	$1,480.00	$740.00

Fee: $____

If an extension of time is required please consider this a petition therefor.

(check and complete the next item, if applicable)

[ ] An extension for _____ months has already been secured and the fee paid therefor of $_____ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $_____

or

[X] Applicant believes that no further extension of term is required. However, if further extensions are necessary, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a further petition and/or fee for extension of time.

5. **TOTAL FEE DUE**

The total fee due is:

Appeal Brief fee:	$165.00
Extension fee (if any):	$_____
Total Fee Due:	**$165.00**

6. **FEE PAYMENT**

[X] Attached is a check in the sum of **$165.00**

[ ] Charge Account No. 23-3000 the sum of $_____, a duplicate of this transmittal is attached.

7. **FEE DEFICIENCY**

[X] If any additional extension and/or fee is required, this is a request therefor to charge Deposit Account No. 23-3000. A duplicate of this transmittal is attached for that purpose.

and/or

[X] If any additional fee for claims is required, charge Deposit Account No. 23-3000. A duplicate of this transmittal is attached for that purpose.

By Beverly A. Lyman
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BRIEF ON APPEAL CERTIFICATE OF MAILING

This Brief is in furtherance of Applicant's Notice of Appeal filed September 19, 2003, appealing the decision of the Examiner dated May 19, 2003 rejecting claims 1-3, 5-11, and 13-16. A copy of the claims appear in Appendix A to this Brief. This Brief is transmitted in triplicate.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail, postage prepaid in an envelope addressed to Mail Stop Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on November 18, 2003.

WOOD, HERRON & EVANS, L.L.P.

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Cincinnati, Ohio 45202 November 18, 2003

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BRIEF ON APPEAL

This is an appeal from the decision of the Examiner in a final Office Action dated May 19, 2003 (paper no. 13). For purpose of appeal, the claims 1-3, 5-11, and 13-16 should read as indicated in Appendix A to this brief.

Real Party in Int r st

The subject application is owned by Renasci, Inc., d/b/a/ Renasci Anti-Aging Center, Scottsdale, Arizona.

Related Appeals and Interferences

None.

Status of the Claims

Original claims 1-18, filed with this application, were rejected in a first Office Action (paper no. 3) dated March 8, 2002, as follows: claims 1 - 18 under 35 U.S.C. §112, ¶ 2; and claims 1, 4-10, 12-14, and 18 under 35 U.S.C. § 102(b) over Chien.

In an Amendment filed April 26, 2002, applicant amended original claims 11, 12 and 17 and added a new method claim 19.

Claims 1-19 were rejected in a final Office Action (paper no. 6) dated July 16, 2002 as follows: claims 1-19 under 35 U.S.C. § 112, ¶ 2; claims 1, 4-10, 12-14, 18, and 19 under 35 U.S.C. § 102(b) over Chien.

In a response dated September 16, 2002 applicant canceled claims 12, 17, and 19, and amended independent claims 1 and 10 as suggested by the Examiner during an interview with applicant's undersigned representative on April 25, 2002, and amended dependent claims 2, 11, and 15.

In an Office Action Summary (paper no. 10) dated December 2, 2002, the Examiner withdrew rejection of claims 1-18 under 35 U.S.C. § 112 ¶ 2 and claims 1, 4-10, 12-14, 18, and 19 under 35 U.S.C. § 102(b) over Chien; the Examiner rejected claims 2, 3, 7, 10, 11, 13, 15, and 16 under 35 U.S.C. § 112 ¶ 2; and rejected claims 1, 4, 7-10, and 13 under 35 U.S.C. § 102(b) over Drake; and rejected claims 1, 4-10, 13, 14, and 18 under 35 U.S.C. § 102(b) over Murray.

In a response dated February 10, 2003 applicant canceled claims 4, 18, and amended dependent claims 7 and 13 and filed an Inventor's Declaration.

In a final Office Action Summary (paper no. 13) dated May 19, 2003, the Examiner withdrew the rejections of claims 7 and 13 under 35 U.S.C. § 112, ¶ 2; withdrew the rejection of claim 4 under 35 U.S.C. §102(b) over Drake; and withdrew the rejection of claims 4 and 18 under 35 U.S.C. §102(b) over Murray. The Examiner maintained rejection of claims 2, 3, 10, 11, 13, 15, and 16 under 35 U.S.C. §112, ¶ 2; rejected claims 1, 7-10 and 13 under 35 U.S.C. §102(b) over Drake; and rejected claims 1, 5-10, 13 and 14 under 35 U.S.C. §102(b) over Murray.

Applicant filed a Notice of Appeal on September 19, 2003 for claims 1-3, 5-11, and 13-16.

Status of Amendments

In a final Office Action dated May 19, 2003, the Examiner rejected claims 2, 3, 10, 11, 13, 15 and 16 as indefinite and claims 1, 5-10, 13 and 14 as anticipated. Applicant filed a Notice of Appeal on September 19, 2003 for claims 1-3, 5-11, and an

Appeal Brief is being timely filed on November 18, 2003. Applicant also timely filed on November 6, 2003, a Supplemental After Final Amendment to correct a typographical error for claim 10 to include a phrase missing in the clean copy but, as the Examiner indicated, was recited in the marked copy of the Amendment filed September 23, 2003.

Summary of the Invention

The inventive method replenishes human growth hormone (hGH) in an adult by first determining the optimal dose for that individual, and then administering that optimal dose as a maintenance dose to replenish hGH. Human growth hormone is the only active administered; there are no other hormones or other actives in the composition (page 3, lines 19-21).

The maintenance dose is determined by administering an initial hGH dose, then determining the individual's response to the initial dose. The individual's initial response may be determined by assaying the level of insulin growth factor-1 (IGF-1), which is produced in response to hGH and mediates the anabolic effects of hGH in adults (page 6, lines 8-15). The initial dose is then serially increased, until a maintenance hGH dose optimized to the individual (page 6, lines 16-25) is determined.

The maintenance dose is then administered. It may be administered on a daily basis. Alternatively, it may be administered on a monthly basis, by calculating the daily dose and taking into account an individual's bioavailability data. The composition may be administered in a time-released formulation, such as a microsphere. This flexibility provides convenience to the individual in terms of dosing.

Issues

Whether claim 2, 3, 10, 11, 13, 15 and 16 are indefinite under 35 U.S.C. § 112, ¶ 2, and whether claims 1, 5-10, 13, and 14 are unpatentable under 35 U.S.C. 102 (b) as anticipated by Drake and Murray.

Grouping of Claims

The rejected claims do not stand together. Each of the two claims sets are rejected on a different statutory basis (claims 2, 3, 10, 11, 13, 15, and 16 as indefinite; claims 1, 5-10, 13, and 14 as anticipated). Whether the claims are found to be indefinite does not affect the proper application of prior art for purposes of anticipation, and whether the claims are found to be anticipated does not affect their definiteness.

Therefore, independent claims 1, 10 and 20, and the claims depending thereon involve different determinations of what is definite, and what is anticipated by the cited art. Accordingly the patentability of these claims involve separate determinations that are independent of each other.

Argument

Claims 2, 3, 10, 11, 13, 15 and 16 are definite under 35 U.S.C. § 112, ¶ 2.

Independent claim 10, and dependent claims 11 and 13, are not indefinite because the missing phrase is included in the claims (see Status of Amendments).

Applicant has filed a Supplemental After Final Amendment on November 6, 2003, as suggested by Examiner during the telephone interview with applicant's undersigned representative on November 3, 2003, to correct a typographical error for claim 10 to include the missing phrase thus conforming the clean and marked-up copies. Applicant notes that the Examiner indicated in the Office Action of May 19, 2003 that the missing phrase was not in the clean copy but was recited in the marked copy of the Amendment filed September 23, 2003.

The standard for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Miles Labs, Inc. v. Shandon,* Inc., 997 F.2d 870 (Fed. Cir. 1993) (Appendix B)). With respect to claims 2, 3, 15, and 16, one skilled in the art would understand the bounds of calculating a daily dose to a monthly dose using individualized bioavailability data.

As stated in the specification, further pointed out in applicant's Declaration (submitted with the Amendment dated February 10, 2003), an individual's response to serially increased doses of hGH are evaluated, usually over one to two months. The dose is adjusted at about two to four week intervals, in a range equal to that of the initial dose. The specification also provides examples of these calculations. It teaches that a male receives an initial dose of 2 µg/kg/day for two to four weeks, then receives a dose of 6 µg/kg/day for two to four weeks, then receives a dose of 8 µg/kg/day for two to four weeks, etc., until the maintenance dose is achieved. It also teaches that a female receives an initial dose of 4 µg/kg/day, then receives a serially increased dose of 8 µg/kg/day for two to four weeks, then receives a dose of 12 µg/kg/day for two to four weeks, etc., until the maintenance dose is achieved.

The maintenance dose is converted from a daily to a monthly dose, based on individualized bioavailability data. One skilled in the art, who had calculated the daily maintenance dose, would know how to convert this information to a monthly dose using bioavailability data. For example, a standard pharmacology text (Goodman and Gilman's The Pharmacological Basis of Therapeutics (Pergamon Press, New York 1990; pp. 5-6, 10-13, 20-32) (Appendix C)) states that bioavailability data indicate the extent to which a drug reaches its site of action, or a biological fluid from which the drug has access to its site of action (page 5). "Individualized bioavailability", as applicant claims, simply encompasses the individual pharmacodyanic and pharmacokinetic parameters of an individual: namely, hepatic and renal clearance (pages 21-23), volume of distribution which relates the amount of drug in the body to concentration of the drug in blood or plasma (pages 23-25), the half-life of a drug in the body (pages 25-26), and the extent and rate of availability which involve the drug's bioavailability and rate of absorption (pages 26-28). These are parameters that one of ordinary skill in this art would use to determine the bounds of these claims.

Thus, applicant's specification as to maintenance or monthly dose, and individualized bioavailability data for making these determinations is definite because one ordinarily skilled in the art would know how to interpret the meaning of these terms.

With respect to Drake and Murray, these are cited as anticipating the invention (35 U.S.C. § 102(b) and § 102(a), respectively). To anticipate, a reference must disclose each and every limitation of the claims. *Transclean Corp. v. Bridgewood Serv.*, 290 F.3d 1364 (Fed. Cir. 2002) (Appendix D)). Neither Drake or Murray disclose

applicant's administration of an individualized dose, and thus do not anticipate applicant's claimed method.

As explained in the Foster Declaration, there is considerable variation in setting the target IGF-1 level to determine the optimal range of hGH. To prevent the harmful results that can ensue, as also explained in the Declaration, the inventive method determines an individualized optimal dose. Neither Drake nor Murray disclose applicant's method for individualizing the optimal hGH replenishing dose selecting a dose producing an optimal replenishment.

Drake does not disclose determining an optimal dose from individualized dosing. Instead, Drake uses a target level of IGF-1 from which he determines his optimal dose. This is not "individualized", in contrast, it is uniform because it has a single target: the IGF-1 level in the upper part of the age-related reference range.

The fact that Drake's dose accounts for age does not make his method of dosing "individualized", because Drake's method would dose to target the same IGF-1 level in all individuals of the same age. However, applicant's method would calculate their individual response to initial and increased doses regardless of whether individuals are the same age, and administer the optimal dose for that individual.

Drake also does not disclose determining a response to a serially increased dose that is predicated on the initial dose that was administered. In Drake's method, there is always the same increase, so that there is no variation in the magnitude.

In contrast, applicant claims an individualized dose where a response to an initial dose is determined, then a response to a serially increase dose is determined,

then the dose that produces optimal replenishment is selected from the serially increased dose and administered as a maintenance dose. This is not disclosed by Drake.

Murray does not anticipate the claimed method. In fact, Murray itself states that "the ideal dosing regimen and determinants of the maintenance dose have, however, yet to be elucidated" (page 537, Summary section). Thus, Murray does not disclose applicant's claimed "optimal response" or "optimal replenishment". The Examiner's rejection, however, contradicts the reference in finding that Murray has, in the Examiner's view, determined the ideal dosing regimen and determinants of the maintenance dose, simply by correlating it with IGF-1 levels. The examiner's view is incorrect on two accounts: (1) it applies Murray in direct contradiction to its express disclosure, and (2) it ignores the individualized dosing requirement of applicant's method to determine an individual's optimal response.

As explained in the Foster Declaration with supporting clinical analysis, the claimed method, which produces an optimal clinical response while avoiding side effects, does in fact reach the "ideal regimen" sought by Murray.

Unless each and every element of a claim is described in a reference, it is error to reject a claim based on that reference. Therefore, applicant's claims are patentable under 35 U.S.C. § 102(b) and § 102(a).

Summary

For the foregoing reasons, appellant believes that the Examiner's rejections of claims 1-3, 5-11, and 13-16 were erroneous, and reversal of the decision is respectfully requested.

Enclosed is a check in the amount of $165.00 for the filing of this Brief. Should any further fees be indicated herein, authorization is given to charge or credit any overpayment to Deposit Account No. 23-3000.

Respectfully submitted,

WOOD, HERRON & EVANS, L.L.P.

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APPENDIX A

1. A method of replenishing human growth hormone (hGH) in an adult human comprising administering a composition consisting essentially of recombinant hGH in an individualized dose to replenish hGH, said individualized dose determined by

(1) determining a response of said human to an initial dose of said composition administered on a daily basis,

(2) thereafter determining a response of said human to serially increased doses of said composition administered on a daily basis,

(3) selecting said dose of composition from (2) producing an optimal replenishment to administer as a maintenance dose, and

(4) thereafter administering said dose from (3) to replenish hGH.

2. The method of claim 1 wherein said maintenance dose is calculated from a daily dose to a monthly dose based on individualized bioavailability data and is administered monthly.

3. The method of claim 2 wherein said dose comprises a microsphere formulation of said agent.

4. CANCELED.

5. The method of claim 1 wherein said human is a male and said maintenance dose is in the range of about 10-14 µg/kg/day.

6. The method of claim 1 wherein said human is a female and said maintenance dose is in the range of about 14-20 µg/kg/day.

7. The method of claim 1 wherein said response comprises increased insulin like growth factor-1 levels.

8. The method of claim 1 wherein said human is a male and said initial dose is about 2 µg/kg/day.

9. The method of claim 1 wherein said human is a female and said initial dose is about 4 µg/kg/day.

10. A method of providing an adult human with human growth hormone (hGH) comprising

administering a composition consisting essentially of recombinant hGH to said human on a daily basis at an initial dose to produce an initial response to said composition,

thereafter administering at least one serially increased initial dose of said composition on a daily basis and evaluating said human's response to said serially increased dose to produce an individualized optimal response to said composition, and

thereafter administering said dose producing said optimal response as a maintenance dose.

11. The method of claim 10 wherein said dose producing said optimal response is calculated from a daily dose to a monthly dose based on individualized bioavailability data and is administered monthly.

12. CANCELED.

13. The method of claim 10 wherein said response is evaluated by evaluating a level of insulin like growth factor-1.

14. A method of optimizing human growth hormone (hGH) replacement in an adult human comprising

(1) administering an initial dose of hGH in the range of about 2 µg/kg/day hGH to about 4 µg/kg/day on a daily basis for about three to four weeks and determining insulin like growth factor 1 (IGF-1) levels,

(2) thereafter administering serially increasing doses of said initial hGH dose on a daily basis for about three to four weeks and determining IGF-1 levels,

(3) selecting said hGH dose from (2) producing optimal hGH replenishment to administer as a maintenance dose, and

(4) thereafter administering said maintenance dose in the range of about 10 µg/kg/day hGH to about 20 µg/kg/day hGH to said individual.

15. The method of claim 14 wherein said maintenance dose is calculated from a daily dose to a monthly dose based on individualized bioavailability data and is administered monthly.

16. The method of claim 15 wherein said maintenance dose comprises hGH formulated in microspheres.

17-19. CANCELED.

APPENDIX B

Miles Labs, Inc. v. Shandon, Inc.,
997 F.2d 870 (Fed. Cir. 1993)

The undisputed evidence is that David Walbert, the same attorney who did most of the work for the State in this case at the rate of $100 per hour, submitted an affidavit in a 1986 proceeding, two years before this one began, that his rate to private clients was $140 per hour, which he swore was below average for attorneys of his skill and expertise. In that same affidavit, Walbert characterized Laughlin McDonald, Brooks' lead counsel in the present case, as "the best known and most respected voting rights attorney in the United States." There was no evidence offered in this case that Walbert's skill, expertise, and career had peaked in 1986 and had been on a sharp downward slide since that time, nor was there any evidence that Walbert had lowered his opinion of his own professional worth or his opinion of McDonald. Under these circumstances, it was clear error for the district court panel to rely so heavily on the rate paid to opposing counsel. We remand the case to it so that the hourly rate can be fixed free of this error.

[10] In reconsidering on remand the hourly rate or rates at which to compensate Brooks' counsel, the court should bear in mind our prior direction that a district court "must explain its reasoning in determining a reasonable attorney's fee to give this court an adequate and informed basis for review." *Gilmere v. City of Atlanta*, 931 F.2d 811, 814 (11th Cir.1991). We have held that the court did not err in setting the range of prevailing rates in this case at $125–$175. In determining the actual rate or rates of compensation within that range for Wilde and McDonald, the court should consider the skill, experience, and reputation of each of the two lawyers, the nature and difficulty of the work performed, and other relevant factors. The court should also consider the hourly rates these two attorneys had been paid in similar litigation at or before the time of this lawsuit. As mentioned previously, Wilde was awarded fees in three other voting rights cases at the rate of $125 per hour. McDonald had been awarded $175 per hour in 1990, but that was the highest amount he had ever been awarded.

We do not mean that the district court panel must necessarily re-open the record on remand; the evidence on these issues appears adequately developed. Nor do we mean to diminish the district court's autho ty to utilize its discretion and its own exp tise in considering these matters and awa ing reasonable attorney's fees. *See Norm* 836 F.2d at 1303 (noting that courts may u own knowledge and experience in determ ing reasonable fees). Indeed, we remand t matter rather than decide it ourselves p cisely because it is the district court pa that has the discretion to exercise, not

III. CONCLUSION

We REMAND this case to the distr court panel for the limited purpose of c recting two aspects of its calculation of att ney's fees. First, the court is to exclu from the number of hours for which comp sation is awarded any hours spent on before December 1, 1989 in opposition preclearance by the Department of Justic Second, the court is to reset, within the $1 to $175 range, the hourly rate for each Brooks' counsel, without regard to the r paid to counsel for the State of Georg After making those two corrections, the co should recalculate the attorney's fees awa and enter an appropriate order.

MILES LABORATORIES, INC. and Triangle Biomedical Equipment, Inc., Plaintiffs/Cross–Appellants,

v.

SHANDON INC. and Shandon Southe Products Limited, Defendants–Appellants.

Nos. 92–1358, 92–1387.

United States Court of Appeals, Federal Circuit.

June 14, 1993.

Rehearing Denied; Suggestion for Rehearing In Banc Declined Sept. 1, 1993.

Action was brought for infringement patent for light microscopy apparatus

8. The same goes for costs associated with such work. See n. 3, above.

tissue processing and patent for processing method. The United States District Court, Western District of Pennsylvania, Gustave Diamond, Chief Judge, held claims of method patent invalid for obviousness, sustained validity of apparatus patent, and found infringement of both patents. On cross appeals, the Court of Appeals, Rader, Circuit Judge, held that: (1) apparatus patent was not invalid for indefiniteness or for failure to meet enablement or utility requirements; (2) accused devices infringed apparatus patent under doctrine of equivalents; (3) claim of method patent addressing means of reusing solutions by returning unused quantities to storage container with pressure was invalid for obviousness; and (4) District Court properly invalidated dependent claims in light of stipulation that claim invalid for obviousness was representative.

Affirmed.

1. Federal Courts ⇐754

Court of Appeals accepts legal conclusions of district court unless incorrect as matter of law. Fed.Rules Civ.Proc.Rule 52(a), 28 U.S.C.A.

2. Federal Courts ⇐776

Court of Appeals does not review de novo proceedings of district court. Fed. Rules Civ.Proc.Rule 52(a), 28 U.S.C.A.

3. Federal Courts ⇐754, 850

To win reversal, party must show that district court committed reversible legal error or relied upon factual findings which were clearly erroneous in light of trial record. Fed.Rules Civ.Proc.Rule 52(a), 28 U.S.C.A.

4. Federal Courts ⇐851, 852

"Clearly erroneous" standard does not entitle Court of Appeals to reverse district court's findings simply because it would have decided case differently; where fact finder's account of evidence is plausible in light of entire record or where it chooses one of two permissible views of evidence, it has committed no clear error. Fed.Rules Civ.Proc.Rule 52(a), 28 U.S.C.A.

See publication Words and Phrases for other judicial constructions and definitions.

5. Patents ⇐314(5)

Compliance with statute requiring patent to be sufficiently definite is question of law. 35 U.S.C.A. § 112.

6. Patents ⇐101(6)

"Distinctly claiming" requirement of statute requiring patents to be sufficiently definite means that claims must have clear and definite meaning when construed in light of complete patent document. 35 U.S.C.A. § 112.

7. Patents ⇐101(6)

Test for definiteness is whether one skilled in art would understand bounds of patent claim when read in light of specification; it is sufficient for purposes of statute that claims read in light of specification reasonably apprise those skilled in art of invention's scope. 35 U.S.C.A. § 112.

8. Patents ⇐101(6)

Degree of precision necessary for adequate patent claims under statute ensuring definiteness of claim language is function of nature of subject matter. 35 U.S.C.A. § 112.

9. Patents ⇐101(6)

Question of whether invention described by claims is operable is irrelevant to issue of whether patent is sufficiently definite. 35 U.S.C.A. § 112.

10. Patents ⇐49

Even if claims of patent for light microscopy tissue processing apparatus did cover only unvented containers, patent was not invalid for lack of utility, as record showed that even unvented containers would be operative; there was testimony that, without vents, collapsible solution containers could permit transfer of fluids by pressure changes. 35 U.S.C.A. § 101.

11. Patents ⇐101(6)

Preferred embodiment described in patent specification for light microscopy tissue processing apparatus disclosed "vented" solution containers and, thus, claims read in light of specification reasonably apprised those skilled in art of claimed invention, as re-

quired to satisfy requirement of definiteness. 35 U.S.C.A. § 112.

12. Patents ⇐101(6)

Patent for light microscopy apparatus for tissue processing disclosed adequate information to enable skilled artisan to make and use claimed invention, particularly as preferred embodiment described in specification disclosed "vented" solution containers. 35 U.S.C.A. § 112.

13. Patents ⇐101(1)

Claim interpretation is first step in two-part infringement determination.

14. Patents ⇐314(5)

Claim interpretation proceeds as question of law.

15. Patents ⇐324.5

When trial resolves factual disputes underlying meaning of claim terms, Court of Appeals reviews those findings under clearly erroneous standard.

16. Patents ⇐167(1), 168(2.1)

In interpreting disputed patent claim terms, trial court considers specification and prosecution history.

17. Patents ⇐226.6

After interpreting patent claim, final step of infringement analysis determines whether accused device is within scope of claim.

18. Patents ⇐226.6, 237

To infringe, accused device must embody exactly each patent claim limitation or its equivalent.

19. Patents ⇐167(1)

Term "cabinet," within meaning of patent claim for light microscopy apparatus for tissue processing, meant single enclosure for various parts of apparatus; embodiment illustrated in patent specification disclosed single cabinet comprised of number of sections, including numerous reagent bottles, processing chamber, paraffin containers and control module.

See publication Words and Phrases for other judicial constructions and definitions.

20. Patents ⇐235(2)

Accused devices in action alleging infringement of patent for light microscopy apparatus for tissue processing did not literally infringe single cabinet limitation of patent, as devices consisted of three modules as opposed to one; term "cabinet," within meaning of claim limitation, meant single enclosure for various parts of apparatus.

21. Patents ⇐237

Accused devices infringed patent for light microscopy apparatus for tissue processing under doctrine of equivalents, even though devices consisted of three modules, as opposed to single cabinet for various components of apparatus; patent did not specify that cabinet contained all components of invention, and devices achieved substantially same result as patent, as they were systems for processing tissue under completely automatic sequence in closed system without requiring substantial movement of specimens.

22. Patents ⇐237

Infringement under doctrine of equivalents requires showing that accused device performs substantially same function, in substantially same way, to achieve substantially same result as claimed device.

23. Patents ⇐237

Doctrine of equivalents prevents pirating of patentee's invention in absence of literal infringement when liability is nevertheless warranted and, thus, doctrine prevents risk of injustice that may result from limited focus on words alone.

24. Patents ⇐237

Limitations on functions of invention in claims, not elements or functions of accused device, establish reference point for doctrine of equivalents.

25. Patents ⇐237

Infringement under doctrine of equivalents does not vanish merely because device performs functions in addition to those performed by claimed device.

26. Patents ⇐16(1), 314(1)

Ultimate legal conclusion of obviousness is question of law, but rests on several factual

inquiries: scope and content of prior art; differences between prior art and claims; level of ordinary skill in art at time of invention; and objective evidence of nonobviousness. 35 U.S.C.A. § 103.

27. Patents ⇐324.5

Court of Appeals reviews factual underpinnings for legal conclusion of obviousness under clearly erroneous standard. 35 U.S.C.A. § 103.

28. Patents ⇐16.17

Claim of patent for light microscopy tissue processing method addressing means of reusing solutions by returning unused quantities to storage container with pressure was invalid for obviousness; prior art of histological equipment taught flow of liquids in tissue processing apparatuses from one location to another with vacuum-pressure, and patent covering electron microscopy tissue processor disclosed processor which discharged used fluids into waste tank, rather than storage container, after processing. 35 U.S.C.A. § 103.

29. Patents ⇐36(1)

Objective indicia of nonobviousness, if present, would have weighed in favor of nonobviousness of patent claim, though lack of such evidence did not weigh in favor of obviousness. 35 U.S.C.A. § 103.

30. Patents ⇐32

Party challenging validity of patent claim, absent pretrial agreement or stipulation, must submit evidence supporting conclusion of invalidity for each contested claim. 35 U.S.C.A. § 282.

31. Patents ⇐314(6)

Where parties stipulate to "representative" claims, validity resolution for representative claims applies to other claims of patent as well. 35 U.S.C.A. § 282.

32. Stipulations ⇐14(1)

In light of stipulation making claim of patent representative for other claims, district court properly invalidated dependent claims upon determining that representative claim was invalid for obviousness. 35 U.S.C.A. § 282.

Arnold Sprung, Sprung Horn Kramer & Woods, Tarrytown, NY, argued for plaintiffs/cross-appellants. With him on the brief was Nathaniel D. Kramer.

Robert D. Yeager, Kirkpatrick & Lockhart, Pittsburgh, PA, argued for defendants-appellants. With him on the brief were Christine R. Ethridge and Melvin C. Snyder, III.

Before PLAGER, Circuit Judge, SMITH, Senior Circuit Judge, and RADER, Circuit Judge.

RADER, Circuit Judge.

Miles Laboratories, Inc. and Triangle Biomedical Equipment, Inc., sued Shandon Inc. and Shandon Southern Products Limited, for infringement of U.S. Patent Reissue No. 29,073, entitled "Light Microscopy Processing Apparatus" ('073),* and U.S. Patent No. 4,001,460, entitled "Light Microscopy Processing Method" ('460). The United States District Court for the Western District of Pennsylvania held claims 1, 2, and 4–7 of the '460 patent invalid for obviousness, sustained the validity of the '073 patent, and found infringement of both patents. *Miles Lab., Inc. v. Shandon, Inc.*, No. 86–2404, 1992 WL 503432 (W.D.Pa. Mar. 11, 1992) (*Miles I*); *Miles Lab., Inc. v. Shandon, Inc.*, No. 86–2404 (W.D.Pa. Apr. 14, 1992) (*Miles II*). Because the record adequately supports the district court's decision, this court affirms.

BACKGROUND

Tissue processing is the treatment of tissue specimens to facilitate viewing them under a microscope. The process exposes the tissue specimens to a series of chemical solutions (reagents) in sequence. The '460 patent claims a method and the '073 patent an apparatus for tissue processing. Except for the claims, the two patents have identical specifications.

* U.S. Patent Reissue No. 29,073 issued on December 14, 1976 as a reissue of U.S. Patent No. 3,892,197, which issued on July 1, 1975.

Under the method accomplished by the apparatus, a central processing chamber confines the tissue specimens under a sealed cover where they remain fixed during treatment with various fluids and paraffin. Once embedded in paraffin, the specimens can be sliced into very thin sections for microscopic viewing. The treatment takes place when a vacuum draws the fluids and paraffin into the central chamber. After proper exposure, pressure in the central chamber expels the fluids back to their storage containers. Thus, the entire processing occurs without tampering with the tissue specimens.

In 1986, Miles sued Shandon for infringement of both patents. The district court held a bench trial in 1988. The district court determined that the doctrine of laches did not bar this action and that claim 1 of the '460 patent was invalid under 35 U.S.C. § 103. *Miles I*, slip. op. at 30. The district court also upheld the validity of the '073 patent and found infringement of both patents. *Id.*

Later, the district court clarified its earlier decision and added the '460 patent's dependent claims 2 and 4–7 to its obviousness ruling. *Miles II*, slip op. at 1. In addition, the district court enjoined Shandon from further infringement of the '073 patent. *Id.* Shandon appeals the validity determination on the '073 patent and the infringement rulings. Miles cross-appeals the invalidity determination on the '460 patent.

DISCUSSION

Standard of Review

[1] This court reviews the district court's fact finding under the "clearly erroneous" standard of Rule 52(a):

> Findings of fact, whether based on oral or documentary evidence, shall not be set aside unless clearly erroneous, and due regard shall be given to the opportunity of the trial court to judge of the credibility of the witnesses.

Fed.R.Civ.P. 52(a) (1988); *see Heisig v. United States*, 719 F.2d 1153, 1158 (Fed.Cir. 1983). This court accepts the legal conclusions of the district court unless incorrect as a matter of law. *Id.*

[2–4] This court does not review *de novo* proceedings of the district court. *Medtronic, Inc. v. Daig Corp.*, 789 F.2d 903, 904, 229 USPQ 664, 666 (Fed.Cir.), *cert. denied*, 479 U.S. 931, 107 S.Ct. 402, 93 L.Ed.2d 355 (1986). To win reversal, a party must show that the district court committed reversible legal error or relied upon factual findings which were clearly erroneous in light of the trial record. *Id.* 789 F.2d at 904–05. In addition, the "clearly erroneous" standard does not entitle this court to reverse the district court's finding simply because it would have decided the case differently. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1375, 231 USPQ 81, 87 (Fed.Cir.1986), *cert. denied*, 480 U.S. 947, 107 S.Ct. 1606, 94 L.Ed.2d 792 (1987). Where the factfinder's account of the evidence is plausible in light of the entire record or where it chooses one of two permissible views of the evidence, it has committed no clear error. *Id.*

The '073 Patent

On the last day of trial, Shandon moved to introduce an infringement defense that the '073 patent was invalid for indefiniteness under 35 U.S.C. § 112, ¶ 2 (1988). The district court, however, upheld the validity of the '073 patent. On appeal, Shandon alleges the claims of the '073 patent omit the requirement for "vented" solution containers and therefore do not distinctly claim the disclosed invention.

Validity

[5, 6] Shandon challenged the claims of the '073 patent as indefinite under § 112, ¶ 2. Compliance with § 112, ¶ 2 is a question of law. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed.Cir.1986). Section 112, paragraph 2, states:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. § 112, ¶ 2. The "distinctly claiming" requirement means that the claims must have a clear and definite meaning when con-

strued in the light of the complete patent document. *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 452, 227 USPQ 293, 296 (Fed.Cir.1985). Section 112 thus ensures definiteness of claim language. *See In re Zletz*, 893 F.2d 319, 322, 13 USPQ2d 1320, 1322 (Fed.Cir.1989).

[7, 8] The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Orthokinetics*, 806 F.2d at 1576. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more. *Hybritech*, 802 F.2d at 1385. The degree of precision necessary for adequate claims is a function of the nature of the subject matter. *Id.*

[9] At trial, a Miles expert, Mr. Kocsis, stated:

> Q Now, reading these claims [of the '073 patent], which we have just discussed, did you see any mention in any of these claims of vented containers or reagent bottles, or anything like that?
>
> A No, I did not.
>
> . . . .
>
> Q Now, that single machine, as described in the '460 and '073 patents, requires that a vent to atmosphere be present in each solution container in order for the machine to transfer solutions from a solution container to a processing chamber and back, is that correct?
>
> A That's correct.

Relying on these isolated statements, Shandon contends that the claims do not specify vented solution containers. Without vented containers, Shandon contends, the claims do not describe a workable invention. Without vents, Shandon asserts, the invention cannot change pressure to draw fluids into and out of the central treatment chamber.

Shandon's argument is irrelevant to definiteness under § 112, ¶ 2. The invention's operability may say nothing about a skilled artisan's understanding of the bounds of the claim. Shandon's argument is possibly relevant, however, to the enablement requirement of § 112, ¶ 1, or to utility under § 101.

[10] Construed as a challenge to utility or enablement, Shandon's argument nevertheless fails. Mr. Kocsis testified that the claimed tissue processors would operate with or without vents in the solution containers. Without vents, collapsible solution containers could permit the transfer of fluids by pressure changes. The district court correctly concluded that "the record shows that even unvented containers would be operative." *Miles II*, slip op. at 4. Thus Shandon did not show a lack of utility, even if the claims cover only unvented containers.

[11, 12] The trial court also determined that the claims, read in light of the specification, covered both unvented containers and vented containers. In fact, the preferred embodiment described in the specification discloses "vented" solution containers:

> Referring again to FIG 3, the previously referred to solution containers 15 (with operating numbers 1 through 10) have respective caps 55 for refilling the containers. Suitable air vents 56, indicated by dashed lines, are provided in each cap 55, but are preferably kept extremely small so as to limit any admission of moisture.

Col. 6, lines 3–9. Therefore, the claims read in light of the specification reasonably apprise those skilled in the art of the claimed invention. Moreover, the record shows that the patent disclosed adequate information to enable a skilled artisan to make and use the claimed invention. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941, 15 USPQ2d 1321, 1329 (Fed.Cir.), *cert. denied*, 498 U.S. 920, 111 S.Ct. 296, 112 L.Ed.2d 250 (1990).

Appellant incorrectly characterized its validity challenge as a claim definiteness issue—a characterization which the district court followed, at least in name. Nonetheless, the district court made proper findings and correctly concluded that appellant did not rebut the presumed validity of the claims.

Infringement

The district court determined that the accused devices, known as the HYPERCENTER and the HYPERCENTER 2, infringed the '073 patent literally, or in the alternative, under the doctrine of equivalents. *Miles I*,

slip op. at 28–30. On appeal, Shandon argues that the district court misconstrued the "cabinet" limitation of the claims.

[13–18] This court reviews a trial court's infringement findings under the "clearly erroneous" standard. *Charles Greiner & Co. v. Mari-Med Mfg., Inc.*, 962 F.2d 1031, 1034, 22 USPQ2d 1526, 1528 (Fed.Cir.1992); *Insta-Foam Prods., Inc. v. Universal Foam Sys., Inc.*, 906 F.2d 698, 702, 15 USPQ2d 1295, 1297 (Fed.Cir.1990). Claim interpretation is the first step in the two-part infringement determination. *Greiner*, 962 F.2d at 1034. Claim interpretation proceeds as a question of law. *Id.* When a trial court, however, resolves factual disputes underlying the meaning of claim terms, this court reviews these findings under the clearly erroneous standard. *Id.* In interpreting disputed claim terms, the trial court considers the specification and the prosecution history. *Id.* After interpreting the claim, the final step of the infringement analysis determines whether the accused device is within the scope of the claim. *Id.* To infringe, an accused device must embody exactly each claim limitation or its equivalent. *Id.*

The district court determined that the HYPERCENTERs contained every limitation set forth in claim 1 of the '073 patent. *Miles I*, slip op. at 28. In reaching this conclusion, the district court construed the cabinet limitation of claim 1 to define an enclosure for the various elements of the processing apparatus. *Id.* The court also determined that the HYPERCENTERs consisted of three modules: a module which housed the operating controls, a module which housed the reagent storage bottles, and a module which contained the central processing chamber and the paraffin baths. The district court concluded that the separate modules of the HYPERCENTER collectively formed a cabinet. *Id.*

[19] The district court properly construed the term "cabinet" to mean a single enclosure for the various parts of the apparatus. The claims, specification, and drawings disclose a single cabinet enclosing the tissue processing apparatus. The embodiment illustrated in the patent specification disclosed a single cabinet comprised of a number of sections, including numerous reagent bottles, a processing chamber, paraffin containers, and a control module. Moreover, Webster's defines "cabinet" as "1 a case or cupboard with drawers or shelves for holding or storing things ... 2 a boxlike enclosure." *Webster's New World Dictionary*, 193 (3d col. ed. 1988).

[20] The HYPERCENTERs, however, consist of three modules as opposed to one. "Module" is defined as "any of a set of units, as cabinets, designed to be arranged or joined in a variety of ways." *Webster's* at 872. Because three does not equal one, the district court clearly erred in finding that the HYPERCENTERs (consisting of three cabinets) literally infringed the single cabinet limitation of the '073 patent.

[21, 22] This court, however, concludes that the district court did not err in determining that the HYPERCENTERs infringed the '073 patent under the doctrine of equivalents. Infringement under the doctrine of equivalents requires a showing that the accused device performs substantially the same function, in substantially the same way, to achieve substantially the same result as the claimed device. *Malta v. Schulmerich Carillons, Inc.*, 952 F.2d 1320, 1325, 21 USPQ2d 1161, 1165 (Fed.Cir.1991), *cert. denied*, —— U.S. ——, 112 S.Ct. 2942, 119 L.Ed.2d 566 (1992) (citing *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608, 70 S.Ct. 854, 856, 94 L.Ed. 1097 (1950)).

[23] The doctrine of equivalents prevents the pirating of the patentee's invention in the absence of literal infringement when liability is nevertheless warranted. *Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1564, 15 USPQ2d 1039, 1044 (Fed. Cir.1990). The doctrine of equivalents thus prevents the risk of injustice that may result from a limited focus on words alone. *Laitram Corp. v. Cambridge Wire Cloth Co.*, 863 F.2d 855, 856–57, 9 USPQ2d 1289, 1291 (Fed. Cir.1988), *cert. denied*, 490 U.S. 1068, 109 S.Ct. 2069, 104 L.Ed.2d 634 (1989).

Shandon argues that the district court did not determine that the HYPERCENTERs achieved "substantially the same result" as

the '073 patent. Shandon contends that the intended result of the '073 patent is unification of the various components. Shandon alleges that HYPERCENTERs achieve safety and operational advantages by separating the components.

The '073 patent achieves an enclosed tissue processing system. The district court stated:

> The '073 patent discloses an *apparatus* for fixing and processing the tissue specimens. It is an improvement over the prior art because it represents the first completely automatic system for allowing light microscopy tissue to be processed under a completely automatic sequence in an entirely closed system and without requiring substantial movement of the specimens.

Miles I, slip op. at 3–4 (citation omitted). This result does not change merely because Shandon separated certain components of the system into discrete modules.

In addition, the '073 patent does not specify that the cabinet contains all components of the invention. Rather claim 1 specifies an "air pump means ... mounted proximate said cabinet." The '073 patent, col. 11, lines 17–19. Claim 1 also claims "electrical control means ... mounted proximate said chamber." *Id.* col. 12, lines 1–3. Therefore, although claim 1 may have a cabinet limitation, not all components of the tissue processor must be within the cabinet. Indeed, the specification states that "the controls could be mounted in a separate cabinet." *Id.* col. 10, lines 34–35.

[24, 25] The limitations and functions of the invention in the claims, not the elements or functions of the accused device, establish the reference point for the doctrine of equivalents. *Insta-Foam*, 906 F.2d at 702. Infringement under the doctrine does not vanish merely because the accused device performs functions in addition to those performed by the claimed device. *Id.* Regardless of separation into modules, Shandon's system is still a "completely automatic system for allowing light microscopy tissue to be processed under a completely automatic sequence in an entirely closed system and without requiring substantial movement of the specimens." *See Miles I*, slip op. at 3–4. Thus, the HYPERCENTERs achieved substantially the same result as the '073 patent.

To allow Shandon to escape infringement simply because it used separate cabinets, as opposed to a single cabinet, is the exact type of injustice the doctrine of equivalents prevents. *See Laitram Corp.*, 863 F.2d at 856–57. This court discerns no clear error in the district court's finding of infringement under the doctrine of equivalents.

The '460 Patent

The district court held claim 1 of the '460 patent invalid for obviousness under 35 U.S.C. § 103 (1988). *Miles I*, slip op. at 16–17. The district court later held the dependent claims of the '460 patent (claims 2, 4–7) invalid by virtue of claim 1's invalidity. *Miles II*, slip op. at 2.

35 U.S.C. § 103—Obviousness

[26, 27] The ultimate legal conclusion of obviousness is a question of law. *Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 989, 6 USPQ2d 1601, 1606 (Fed.Cir.1988). The analysis of obviousness, however, rests on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the art at the time of invention; and (4) objective evidence of nonobviousness. *Id.* (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18, 86 S.Ct. 684, 693–694, 15 L.Ed.2d 545 (1966)). This court reviews these factual underpinnings for the legal conclusion of obviousness under the "clearly erroneous" standard. *Specialty Composites*, 845 F.2d at 989. The facts stated herein are based on district court findings not found to be clearly erroneous or otherwise not in dispute.

[28] The prior art in this instance included U.S. Patent No. 3,526,203 (the '203 patent), U.S. Patent No. 3,227,130 (the Weiskopf patent), and the Lipshaw Manufacturing Corporation's "Fluid X Changer." The '203 patent covers an electron microscopy tissue processor. Electron microscopy differs from light microscopy in that the former requires only very small tissue specimens. With

small tissue specimens, electron microscopy does not need to reuse processing reagents. Nonetheless, the specification of the '203 patent provides: "it will be apparent that the processor of the invention may be used for processing the larger sized tissue particles which are intended for light microscopy examination." *Miles I*, slip op. at 10 (quoting U.S. Patent No. 3,526,203, col. 8, lines 5–8). The claims of the '203 patent disclose the vacuum component of the '460 patent. Furthermore, the '203 patent suggests a solution to the problem resolved by claim 1 of the '460 patent, namely, a means of reusing a solution by returning unused quantities to the storage container with pressure.

The specification of the '203 patent provides:

> In this regard it should be noted that the practice in electron microscopy work is not to reuse the solutions and in the system of the invention only fresh solution is transferred through the lines and valves connecting the containers with the processing chamber. If the particular solutions are required to be pumped back to the containers after use appropriate pumping and switching controls would have to be provided.

U.S. Patent No. 3,526,203, col. 8, lines 12–19. Although electron microscopy does not reuse solutions, the '203 patent suggests to a skilled artisan the reuse of solutions by pumping them back to their storage containers.

The "Fluid X Changer" (a device used for staining slides bearing tissue specimens) also suggests transfer of solutions by pressure. Moreover, the Weiskopf patent discloses a tissue processor which transfers solutions by pressure controls. Thus, the prior art of histological equipment taught the flow of liquids in tissue processing apparatuses from one location to another with vacuum-pressure.

The differences between the prior art and claim 1 of the '406 patent were minor and achievable by simple modification. Moreover, the prior art references collectively suggest the engineering necessary to achieve these modifications. Simply put, the '203 patent discloses a tissue processor which does not reuse fluids but instead discharges them into a waste tank after processing. By running a line from the processing chamber back to the fluid storage containers (rather than to the waste tank), the '203 patent would anticipate the '460 patent.

[29] The level of ordinary skill in the art suggests as well a thorough knowledge of the principles of fluid transfer using pressure-vacuum pumps, valves, and conduits at the time of the '460 patent's development. Finally, Miles did not show objective indicia of non-obviousness. Such evidence, if present, would weigh in favor of non-obviousness, although the lack of such evidence does not weigh in favor of obviousness. *See, e.g., Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 1 USPQ2d 1196, 1199 (Fed.Cir.1986). Miles presented no evidence, for instance, that its device represented a substantial share of any definable market. Miles also did not offer evidence on factors such as long-felt need or teaching away in the prior art.

In sum, the district court concluded:

> On the basis of the *Graham* test, therefore, we conclude that claim 1 of the '460 patent is invalid under 35 U.S.C. § 103 because the subject matter of claim 1 as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains.

Miles I, slip op. at 16–17. This court finds no error (and certainly no clear error) with the district court's obviousness findings and conclusion. Therefore this court affirms the district court's determination of invalidity of claim 1 of the '460 patent.

[30, 31] In its later opinion, the district court clarified its earlier decision and also held dependent claims (2 and 4–7) of the '460 patent invalid. *Miles II*, slip op. at 1–2. Section 282 requires an independent analysis of the validity of each claim. 35 U.S.C. § 282 (1988); *Ortho Pharmaceutical Corp. v. Smith*, 959 F.2d 936, 942, 22 USPQ2d 1119, 1124 (Fed.Cir.1992). A party challenging the validity of a claim, absent a pretrial agreement or stipulation, must submit evidence

supporting a conclusion of invalidity for each contested claim. *Id.* Where the parties stipulate to "representative" claims, however, a validity resolution for the representative claims applies to the other claims as well. *See Panduit Corp. v. Dennison Mfg. Co.*, 836 F.2d 1329, 1330–31, 5 USPQ2d 1266, 1267–68 (Fed.Cir.1987).

[32] In an April 1988 pretrial "Stipulation of Agreed Fact, Law of the Case and Questions of Law," the parties agreed:

> The '460 patent contains seven claims. Claim 1 is the only independent claim. Claims 2 through 7 depend directly or indirectly from claim 1. Consequently, claim 1 is the broadest claim and can be considered to be representative of the claims in this patent.

Miles II, slip op. at 2 n. 1. This stipulation of the parties made claim 1 a representative for the other claims in the patent. Thus, the parties, their counsel, and the trial court understood that the result the court reached for claim 1 would bind all other claims. Therefore, this court affirms the district court's invalidation of the dependent claims of the '460 patent.

The district court also determined that the accused device infringed the '460 patent. Because it affirms the district court's invalidity findings, this court need not reach the district court's infringement determination. *See Dana Corp. v. IPC Ltd. Partnership*, 860 F.2d 415, 417, 8 USPQ2d 1692, 1694 (Fed. Cir.1988), *cert. denied*, 490 U.S. 1067, 109 S.Ct. 2068, 104 L.Ed.2d 633 (1989).

CONCLUSION

For the above stated reasons, this court affirms the district court's finding of infringement of the '073 patent and the upholding of its validity. This court also affirms the district court's holding that claims 1, 2, and 4–7 of the '460 patent are invalid due to obviousness.

COSTS

Each party shall bear its own costs for this appeal.

AFFIRMED.

APPENDIX C

Goodman and Gilman's
The Pharmacological Basis of Therapeutics
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GOODMAN and GILMAN's

The Pharmacological Basis of Therapeutics

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In this textbook, reference to proprietary names of drugs is ordinarily made only in chapter sections dealing with preparations. Such names are given in SMALL-CAP TYPE, usually immediately following the official or nonproprietary titles. Proprietary names of drugs also appear in th Index.

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to a steady state. For a weak base with a pK_a of 4.4 ($BH^+ \rightleftharpoons B + H^+$), the ratio would be reversed, as would the thick horizontal arrows in Figure 1–2, which indicate the predominant species at each pH. These considerations have obvious implications for the absorption and excretion of drugs, as will be discussed more specifically below. The establishment of concentration gradients of weak electrolytes across membranes with a pH gradient is a purely physical process and does not require an active transport system. All that is necessary is a membrane preferentially permeable to one form of the weak electrolyte and a pH gradient across the membrane. The establishment of the pH gradient is, however, an active process.

Bulk flow through intercellular pores is the major mechanism of passage of drugs across most capillary endothelial membranes, with the important exception of the central nervous system (CNS) (*see* below). These intercellular gaps are sufficiently large that diffusion across most capillaries is limited by blood flow and not by the lipid solubility of drugs or pH gradients. This is an important factor in filtration across glomerular membranes in the kidney (*see* below). Tight junctions are characteristic of capillaries of the CNS and a variety of epithelia. Intercellular diffusion is consequently limited. Pinocytosis, the formation and movement of vesicles across cell membranes, has been implicated in drug absorption. However, the quantitative significance of pinocytosis is questionable.

Carrier-Mediated Membrane Transport. While passive diffusion through the bilayer is dominant in the absorption and distribution of most drugs, more active and selective mechanisms can play important roles. Active transport of some drugs occurs across neuronal membranes, the choroid plexus, renal tubular cells, and hepatocytes. The characteristics of active transport—selectivity, competitive inhibition by congeners, a requirement for energy, saturability, and movement against an electrochemical gradient—may be important in the mechanism of action of drugs that are subject to active transport or that interfere with the active transport of natural metabolites or neurotransmitters. The term *facilitated diffusion* describes a carrier-mediated transport process to which there is no input of energy, and movement of the substance in question thus cannot occur against an electrochemical gradient. Such mechanisms, which may also be highly selective for specific conformational structures of drugs, are necessary for the transport of endogenous compounds whose rate of movement across biological membranes by simple diffusion would otherwise be too slow.

DRUG ABSORPTION, BIOAVAILABILITY, AND ROUTES OF ADMINISTRATION

Absorption describes the rate at which a drug leaves its site of administration and the extent to which this occurs. However, the clinician is primarily concerned with a parameter designated as *bioavailability*, rather than absorption. Bioavailability is a term used to indicate the extent to which a drug reaches its site of action *or* a biological fluid from which the drug has access to its site of action. For example, a drug that is absorbed from the stomach and intestine must first pass through the liver before it reaches the systemic circulation. If the drug is metabolized in the liver or excreted in the bile, some of the active drug will be inactivated or diverted before it can reach the general circulation and be distributed to its sites of action. If the metabolic or excretory capacity of the liver for the agent in question is great, bioavailability will be substantially decreased (the so-called first-pass effect). This decrease in availability is a function of the anatomical site from which absorption takes place; other anatomical, physiological, and pathological factors can influence bioavailability (*see* below), and the choice of the route of drug administration must be based on an understanding of these conditions. Moreover, factors that modify the absorption of a drug can change its bioavailability.

Factors That Modify Absorption. Many variables, in addition to the physicochemical factors that affect transport across membranes, influence the absorption of drugs. Absorption, regardless of the site, is dependent upon drug solubility. Drugs given in aqueous solution are more rapidly absorbed than those given in oily solution, suspension, or solid form because they mix more readily with the aqueous phase at the absorptive site. For those given in solid form, the rate of dissolution may be the lim-

iting factor in their absorption. Local conditions at the site of absorption alter solubility, particularly in the gastrointestinal tract. Aspirin, which is relatively insoluble in acidic gastric contents, is a common example of such a drug. The concentration of a drug influences its rate of absorption. Drugs ingested or injected in solutions of high concentration are absorbed more rapidly than are drugs in solutions of low concentration. The circulation to the site of absorption also affects drug absorption. Increased blood flow, brought about by massage or local application of heat, enhances the rate of drug absorption; decreased blood flow, produced by vasoconstrictor agents, shock, or other disease factors, can slow absorption. The area of the absorbing surface to which a drug is exposed is one of the more important determinants of the rate of drug absorption. Drugs are absorbed very rapidly from large surface areas such as the pulmonary alveolar epithelium, the intestinal mucosa, or, in a few cases after extensive application, the skin. The absorbing surface is determined largely by the route of administration. Each of these factors separately or in conjunction with one another may have profound effects on the efficacy and toxicity of a drug.

Enteral (Oral) vs. Parenteral Administration. Often there is a choice of the route by which a therapeutic agent may be given, and a knowledge of the advantages and disadvantages of the different routes of administration is then of primary importance. Some characteristics of the major routes employed for systemic drug effect are compared in Table 1–1.

Oral ingestion is the most common method of drug administration. It is also the safest, most convenient, and most economical. Disadvantages to the oral route include the incapability to absorb some drugs because of their physical characteristics (*e.g.*, polarity), emesis as a result of irritation to the gastrointestinal mucosa, destruction of some drugs by digestive enzymes or low gastric pH, irregularities in absorption or propulsion in the presence of food or other drugs, and necessity for cooperation on the part of the patient. In addition, drugs in the gastrointestinal tract may be metabolized by the enzymes of the mu-

Table 1–1. SOME CHARACTERISTICS OF COMMON ROUTES OF DRUG ADMINISTRATION *

ROUTE	ABSORPTION PATTERN	SPECIAL UTILITY	LIMITATIONS AND PRECAUTIONS
Intravenous	Absorption circumvented Potentially immediate effects	Valuable for emergency use Permits titration of dosage Suitable for large volumes and for irritating substances, when diluted	Increased risk of adverse effects Must inject solutions *slowly*, as a rule Not suitable for oily solutions or insoluble substances
Subcutaneous	Prompt, from aqueous solution Slow and sustained, from repository preparations	Suitable for some insoluble suspensions and for implantation of solid pellets	Not suitable for large volumes Possible pain or necrosis from irritating substances
Intramuscular	Prompt, from aqueous solution Slow and sustained, from repository preparations	Suitable for moderate volumes, oily vehicles, and some irritating substances	Precluded during anticoagulant medication May interfere with interpretation of certain diagnostic tests (*e.g.*, creatine kinase)
Oral ingestion	Variable; depends upon many factors (*see* text)	Most convenient and economical; usually more safe	Requires patient cooperation Availability potentially erratic and incomplete for drugs that are poorly soluble, slowly absorbed, unstable, or extensively metabolized by the liver

* *See* text for more complete discussion and for other routes.

pass metabolism after oral administration (*see* Ridout *et al.*, 1988).

Eye. Topically applied ophthalmic drugs are used primarily for their local effects. Systemic absorption that results from drainage through the nasolacrimal canal is usually undesirable. In addition, drug that is absorbed after such drainage is not subject to first-pass hepatic elimination. Unwanted systemic pharmacological effects may occur for this reason when β-adrenergic antagonists are administered as ophthalmic drops. Local effects usually require absorption of the drug through the cornea; corneal infection or trauma may thus result in more rapid absorption. Ophthalmic delivery systems that provide prolonged duration of action (*e.g.*, suspensions and ointments) are useful additions to ophthalmic therapy. Ocular inserts, developed more recently, provide continuous delivery of low amounts of drug. Very little is lost through drainage; hence, systemic side effects are minimized.

Bioequivalence. Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration. Two pharmaceutically equivalent drug products are considered to be bioequivalent when the rates and extents of bioavailability of the active ingredient in the two products are not significantly different under suitable test conditions. In the past, dosage forms of a drug from different manufacturers and even different lots of preparations from a single manufacturer sometimes differed in their bioavailability. Such differences were seen primarily among oral dosage forms of poorly soluble, slowly absorbed drugs. They result from differences in crystal form, particle size, or other physical characteristics of the drug that are not rigidly controlled in formulation and manufacture of the preparations. These factors affect disintegration of the dosage form and dissolution of the drug and hence the rate and extent of drug absorption.

The potential nonequivalence of different drug preparations is a matter of concern. Strengthened regulatory requirements over the past few years have resulted in significantly fewer documented cases of nonequivalence between approved drug products. However, since equivalence of measured systemic concentrations of active drug and known metabolites is not necessarily proof of therapeutic equivalence, some clinicians prefer to maintain certain "fragile" patients on a single manufacturer's product. The significance of possible nonequivalence of drug preparations is further discussed in connection with drug nomenclature and the choice of drug name in writing prescription orders (*see* Appendix I).

DISTRIBUTION OF DRUGS

After a drug is absorbed or injected into the bloodstream, it may be distributed into interstitial and cellular fluids. Patterns of drug distribution reflect certain physiological factors and physicochemical properties of drugs. An initial phase of distribution may be distinguished that reflects cardiac output and regional blood flow. Heart, liver, kidney, brain, and other well perfused organs receive most of the drug during the first few minutes after absorption. Delivery of drug to muscle, most viscera, skin, and fat is slower, and these tissues may require several minutes to several hours before steady state is attained. A second phase of drug distribution may therefore be distinguished; this is also limited by blood flow, and it involves a far larger fraction of the body mass than does the first phase. Superimposed on patterns of distribution of blood flow are factors that determine the rate at which drugs diffuse into tissues. Diffusion into the interstitial compartment occurs rapidly because of the highly permeable nature of capillary endothelial membranes (except in the brain). Lipid-insoluble drugs that permeate membranes poorly are restricted in their distribution and hence in their potential sites of action. Distribution may also be limited by drug binding to plasma proteins, particularly albumin for acidic drugs and α_1-acid glycoprotein for basic drugs. An agent that is extensively and strongly bound has limited access to cellular sites of action, and it may be metabolized and eliminated slowly. Drugs may accumulate in tissues in higher concentrations than would be expected from diffusion equilibria as a result of pH gradients, binding to intracellular constituents, or partitioning into lipid.

Drug that has accumulated in a given tissue may serve as a reservoir that prolongs drug action in that same tissue or at a distant site reached through the circulation. An example that illustrates many of these factors is the use of the intravenous anesthetic thiopental, a highly lipid-soluble drug. Because blood flow to the brain is so high, the drug reaches its maximal concentration in brain within a minute after it is injected intravenously. After injection is concluded, the plasma concentration falls as thiopental diffuses into other tissues, such as muscle. The concentration of the drug in brain follows that of the plasma,

because there is little binding of the drug to brain constituents. Thus, onset of anesthesia is rapid, but so is its termination. Both are directly related to the concentration of drug in the brain. A third phase of distribution for this drug is due to the slow, blood-flow–limited uptake by fat. With administration of successive doses of thiopental, accumulation of drug takes place in fat and other tissues that can store large amounts of the compound. These can become reservoirs for the maintenance of the plasma concentration, and, therefore the brain concentration, at or above the threshold required for anesthesia. Thus, a drug that is short acting because of rapid redistribution to sites at which the agent has no pharmacological action can become long acting when these storage sites are "filled" and termination of the drug's action becomes dependent on biotransformation and excretion (*see* Benet, 1978).

Since the difference in pH between intracellular and extracellular fluids is small (7.0 vs. 7.4), this factor can result in only a relatively small concentration gradient of drug across the plasma membrane. Weak bases are concentrated slightly inside of cells, while the concentration of weak acids is slightly lower in the cells than in extracellular fluids. Lowering the pH of extracellular fluid increases the intracellular concentration of weak acids and decreases that of weak bases, provided that the intracellular pH does not also change and that the pH change does not simultaneously affect the binding, biotransformation, or excretion of the drug. Elevating the pH produces the opposite effects (*see* Figure 1–2).

Central Nervous System and Cerebrospinal Fluid. The distribution of drugs to the CNS from the bloodstream is unique, mainly in that entry of drugs into the cerebrospinal fluid and extracellular space of the CNS is restricted. The restriction is similar to that across the gastrointestinal epithelium. Endothelial cells of the brain capillaries differ from their counterparts in most tissues by the absence of intercellular pores and pinocytotic vesicles. Tight junctions predominate, and aqueous bulk flow is thus severely restricted. This is not unique to the CNS capillaries (tight junctions appear in many muscle capillaries as well). It is likely that the unique arrangement of pericapillary glial cells also contributes to the slow diffusion of organic acids and bases into the CNS. The drug molecules probably must traverse not only endothelial but also perivascular cell membranes before reaching neurons or other target cells in the CNS. Cerebral blood flow is the only limitation to permeation of the CNS by highly lipid-soluble drugs. With increasing polarity the rate of diffusion of drugs into the CNS is proportional to the lipid solubility of the nonionized species. Strongly ionized agents such as quaternary amines are normally unable to enter the CNS from the circulation.

In addition, organic ions are extruded from the cerebrospinal fluid into blood at the choroid plexus by transport processes similar to those in the renal tubule. Lipid-soluble substances leave the brain by diffusion through the capillaries and the blood–choroid plexus boundary. Drugs and endogenous metabolites, regardless of lipid solubility and molecular size, also exit with bulk flow of the cerebrospinal fluid through the arachnoid villi.

The blood–brain barrier is adaptive in that exclusion of drugs and other foreign agents such as penicillin or tubocurarine protects the CNS against severely toxic effects. However, the barrier is neither absolute nor invariable. Very large doses of penicillin may produce seizures; meningeal or encephalic inflammation increases the local permeability. Maneuvers to increase permeability of the blood–brain barrier are potentially important to enhance the efficacy of chemotherapeutic agents that are used to treat infections or tumors localized in the brain.

Drug Reservoirs. As mentioned, the body compartments in which a drug accumulates are potential reservoirs for the drug. If stored drug is in equilibrium with that in plasma and is released as the plasma concentration declines, a concentration of the drug in plasma and at its locus of action is sustained, and pharmacological effects of the drug are prolonged. However, if the reservoir for the drug has a large capacity and fills rapidly, it so alters the distribution of the drug that larger quantities of the drug are required initially to provide a therapeutically effective concentration in the target organ.

Plasma Proteins. Many drugs are bound to plasma proteins, mostly to plasma albumin for acidic drugs and to α_1-acid glycoprotein for basic drugs; binding to other plasma proteins generally occurs to a much smaller extent. The binding is usually reversible; covalent binding of reactive drugs

such as alkylating agents occurs occasionally.

The fraction of total drug in plasma that is bound is determined by the drug concentration, its affinity for the binding sites, and the number of binding sites. Simple mass-action equations are used to describe the free and bound concentrations (*see* Chapter 2). At low concentrations of drug (less than the plasma protein–binding dissociation constant), the fraction bound is a function of the concentration of binding sites and the dissociation constant. At high drug concentrations (greater than the dissociation constant), the fraction bound is a function of the number of binding sites and the drug concentration. Therefore, statements that a given drug is bound to a specified extent apply only over a limited range of concentrations. The percentage values listed in Appendix II refer only to the therapeutic range of concentrations for each drug.

Binding of a drug to plasma proteins limits its concentration in tissues and at its locus of action, since only unbound drug is in equilibrium across membranes. Binding also limits glomerular filtration of the drug, since this process does not immediately change the concentration of free drug in the plasma (water is also filtered). However, plasma protein binding does *not* generally limit renal tubular secretion or biotransformation, since these processes lower the free drug concentration, and this is rapidly followed by dissociation of the drug–protein complex. If a drug is avidly transported or metabolized and its clearance, calculated on the basis of unbound drug, exceeds organ plasma flow, binding of the drug to plasma protein may be viewed as a transport mechanism that fosters drug elimination by delivering drug to sites for elimination.

Since binding of drugs to plasma proteins is rather nonselective, many drugs with similar physicochemical characteristics can compete with each other and with endogenous substances for these binding sites. For example, displacement of unconjugated bilirubin from binding to albumin by the sulfonamides and other organic anions is known to increase the risk of bilirubin encephalopathy in the newborn, and drug toxicity has sometimes been attributed to similar competition between drugs for binding sites. Such interactions are often more complex than generally stated. Since drug displaced from plasma protein will redistribute into its full potential volume of distribution, the concentration of free drug in plasma and tissues after redistribution may be increased only slightly. The interaction may also involve altered elimination of the drug. Risk of adverse effect is greatest if the displaced drug has a limited volume of distribution, if the competition extends to the drug bound in tissues, if elimination of the drug is also reduced, or if the displacing drug is administered in high dosage by rapid intravenous injection. Competition of drugs for plasma protein-binding sites may also cause misinterpretation of measured concentrations of drugs in plasma, since most assays do not distinguish free from bound drug.

Cellular Reservoirs. Many drugs accumulate in muscle and other cells in higher concentrations than in the extracellular fluids. If the intracellular concentration is high and if the binding is reversible, the tissue involved may represent a sizable drug reservoir, particularly if the tissue represents a large fraction of body mass. For example, during long-term administration of the antimalarial agent quinacrine, the concentration of the drug in liver may be several thousand times that in plasma. Accumulation in cells may be the result of active transport or, more commonly, binding. Tissue binding of drugs usually occurs to proteins, phospholipids, or nucleoproteins and is generally reversible.

Fat as a Reservoir. Many lipid-soluble drugs are stored by physical solution in the neutral fat. In obese persons, the fat content of the body may be as high as 50%, and even in starvation it constitutes 10% of body weight; hence, fat can serve as an important reservoir for lipid-soluble drugs. For example, as much as 70% of the highly lipid-soluble barbiturate thiopental may be present in body fat 3 hours after administration. However, fat is a rather stable reservoir because it has a relatively low blood flow.

Bone. The tetracycline antibiotics (and other divalent-metal-ion chelating agents) and heavy metals may accumulate in bone by adsorption onto the bone-crystal surface and eventual incorporation into the crystal lattice. Bone can become a reservoir for the slow release of toxic agents such as lead or radium into the blood. Their effects can

thus persist long after exposure has ceased. Local destruction of the bone medulla may also lead to reduced blood flow and prolongation of the reservoir effect, since the toxic agent becomes sealed off from the circulation; this may further enhance the direct local damage to the bone. A vicious cycle results whereby the greater the exposure to the toxic agent the slower is its rate of elimination.

Transcellular Reservoirs. Drugs also cross epithelial cells and may accumulate in the transcellular fluids. The major transcellular reservoir is the gastrointestinal tract. Weak bases are passively concentrated in the stomach from the blood, because of the large pH differential between the two fluids, and some drugs are secreted in the bile in an active form or as a conjugate that can be hydrolyzed in the intestine. In these cases, and when an orally administered drug is slowly absorbed, the gastrointestinal tract serves as a drug reservoir.

Other transcellular fluids, including cerebrospinal fluid, aqueous humor, endolymph, and joint fluids, do not generally accumulate significant total amounts of drugs.

Redistribution. Termination of drug effect is usually by biotransformation and excretion, but it may also result from redistribution of the drug from its site of action into other tissues or sites. Redistribution is a factor in terminating drug effect primarily when a highly lipid-soluble drug that acts on the brain or cardiovascular system is administered rapidly by intravenous injection or by inhalation. The factors involved in redistribution of drugs have been discussed above.

Placental Transfer of Drugs. The potential transfer of drugs across the placenta is important, since drugs may cause congenital anomalies. Administered immediately before delivery, they may also have adverse effects on the neonate. Drugs cross the placenta primarily by simple diffusion. Lipid-soluble, nonionized drugs readily enter the fetal blood from the maternal circulation. Penetration is least with drugs possessing a high degree of dissociation or low lipid solubility. The view that the placenta is a barrier to drugs is inaccurate. A more appropriate approximation is that the fetus is to at least some extent exposed to essentially all drugs taken by the mother.

BIOTRANSFORMATION OF DRUGS

The physicochemical properties of drug molecules that permit rapid passage across cellular membranes during absorption and distribution also impair subsequent excretion. For example, after filtration at the renal glomerulus most lipid-soluble drugs largely escape excretion from the body because they are readily reabsorbed from the filtrate by diffusion through the renal tubular cells. Thus, the enzymatic biotransformation of drugs to more polar and less lipid-soluble metabolites enhances their excretion and reduces their volume of distribution. Such biotransformation relieves the burden of foreign chemicals and is critical for the survival of the organism. Studies of the genes that encode the enzymes of biotransformation have led to the view that they evolved millions of years ago as a mechanism for removal of natural constituents of foods, such as flavones, terpenes, steroids, and alkaloids. (For excellent summaries of drug biotransformation, *see* Goldstein *et al.*, 1974; Lee *et al.*, 1977; Jacqz *et al.*, 1986; Nebert and Gonzalez, 1987.)

Enzymes Responsible for Biotransformation. The enzyme systems responsible for the biotransformation of many drugs are located in the smooth endoplasmic reticulum of the liver (operationally designated the microsomal fraction). These enzymes also are present in other organs, such as the kidney, lung, and gastrointestinal epithelium, although in smaller quantities. Drugs absorbed from the intestine may thus be subject to the first-pass effect. This represents the combined action of hepatic and gastrointestinal epithelial enzymes, which can at times prevent effective concentrations of active drug from reaching the systemic circulation after oral administration, as discussed above.

The chemical reactions of enzymatic biotransformation are classified as either phase-I or phase-II reactions. Phase-I reactions convert the parent drug to a more polar metabolite by oxidation, reduction, or hydrolysis. The resulting metabolite may be pharmacologically inactive, less active, or occasionally more active than the parent molecule. When the metabolite itself is the active drug, the parent compound is said to be a *prodrug* (*e.g.*, enalapril). Phase-II reactions, which are also called conjugation

linization or acidification of the urine. Whether alteration of urine pH results in significant change in drug elimination depends upon the extent and persistence of the pH change and the contribution of pH-dependent passive reabsorption to total drug elimination. The effect is greatest for weak acids and bases with pK_a values in the range of urinary pH (5 to 8). However, alkalinization of urine can produce a fourfold to sixfold increase in excretion of a relatively strong acid such as salicylate when urinary pH is changed from 6.4 to 8.0. The fraction of nonionized drug would decrease from 1% to 0.04%.

Biliary and Fecal Excretion. Many metabolites of drugs formed in the liver are excreted into the intestinal tract in the bile. These metabolites may be excreted in the feces; more commonly, they are reabsorbed into the blood and ultimately excreted in the urine. Both organic anions, including glucuronides, and organic cations are actively transported into bile by carrier systems similar to those that transport these substances across the renal tubule. Both transport systems are nonselective, and ions of like charge may compete for transport. Steroids and related substances are transported into bile by a third carrier system. The effectiveness of the liver as an excretory organ for glucuronide conjugates is very much limited by their enzymatic hydrolysis after the bile is mixed with the contents of the small intestine, and the parent drug can be reabsorbed from the intestine. Thus, such compounds may undergo extensive biliary cycling with eventual excretion by the kidney.

Excretion by Other Routes. Excretion of drugs into sweat, saliva, and tears is quantitatively unimportant. Elimination by these routes is dependent mainly upon diffusion of the nonionized, lipid-soluble form of drugs through the epithelial cells of the glands and is pH dependent. Reabsorption of the nonionized drug from the primary secretion probably also occurs in the ducts of the glands, and active secretion of drugs across the ducts of the gland may also occur. Drugs excreted in the saliva enter the mouth, where they are usually swallowed. The concentration of some drugs in saliva parallels that in plasma. Saliva may therefore be a useful biological fluid in which to determine drug concentrations when it is difficult or inconvenient to obtain blood.

The same principles apply to excretion of drugs in breast milk. Since milk is more acidic than plasma, basic compounds may be slightly concentrated in this fluid, and the concentration of acidic compounds in the milk is lower than in plasma. Nonelectrolytes, such as ethanol and urea, readily enter breast milk and reach the same concentration as in plasma, independent of the pH of the milk. (*See* Atkinson *et al.*, 1988.)

Although excretion into hair and skin is also quantitatively unimportant, sensitive methods of detection of toxic metals in these tissues have forensic significance. Arsenic in Napoleon's hair, detected 150 years after administration, has raised interesting questions about how he died, and by whose hand. Mozart's manic behavior during the preparation of his last major work, the *Requiem*, may have been due to mercury poisoning; traces of the metal have been found in his hair.

CLINICAL PHARMACOKINETICS

A fundamental hypothesis of clinical pharmacokinetics is that a relationship exists between the pharmacological or toxic response to a drug and the concentration of the drug in a readily accessible site in the body (*e.g.*, blood). This hypothesis has been documented for many drugs (*see* Appendix II), although it is apparent for some drugs that no clear or simple relationship has been found between pharmacological effect and concentration in plasma. In most cases, as depicted in Figure 1–1, the concentration of drug in the systemic circulation will be related to the concentration of drug at its sites of action. The pharmacological effect that results may be the clinical effect desired, a toxic effect, or, in some cases, an effect unrelated to efficacy or toxicity. Clinical pharmacokinetics attempts to provide both a more quantitative relationship between dose and effect and the framework with which to interpret measurements of concentrations of drugs in biological fluids. The importance of pharmacokinetics in patient care rests on the improvement in efficacy that can be attained by attention to its principles when dosage regimens are chosen and modified.

The various physiological and pathophysiological variables that dictate adjustment of dosage in individual patients often do so as a result of modification of pharmacokinetic parameters. The three most important parameters are *clearance*, a measure of the body's ability to eliminate drug;

volume of distribution, a measure of the apparent space in the body available to contain the drug; and *bioavailability*, the fraction of drug absorbed as such into the systemic circulation. Of lesser importance are the *rates* of availability and distribution of the agent.

CLEARANCE

Clearance is the most important concept to be considered when a rational regimen for long-term drug administration is to be designed. The clinician usually wants to maintain steady-state concentrations of a drug within a known therapeutic range (*see* Appendix II). Assuming complete bioavailability, the steady state will be achieved when the rate of drug elimination equals the rate of drug administration:

$$\text{Dosing rate} = CL \cdot C_{ss} \quad (1)$$

where CL is clearance and C_{ss} is the steady-state concentration of drug. Thus, if the desired steady-state concentration of drug in plasma or blood is known, the rate of clearance of drug by the patient will dictate the rate at which the drug should be administered.

The concept of clearance is extremely useful in clinical pharmacokinetics because clearance of a given drug is usually constant over the range of concentrations encountered clinically. This is true because systems for elimination of drugs are not usually saturated and, thus, the *absolute* rate of elimination of the drug is essentially a linear function of its concentration in plasma. A synonymous statement is that the elimination of most drugs follows first-order kinetics—a constant *fraction* of drug is eliminated per unit of time. If mechanisms for elimination of a given drug become saturated, the kinetics become zero-order—a constant *amount* of drug is eliminated per unit of time. Under such a circumstance, clearance becomes variable. Principles of drug clearance are similar to those of renal physiology, where, for example, creatinine clearance is defined as the rate of elimination of creatinine in the urine relative to its concentration in plasma. At the simplest level, clearance of a drug is the rate of elimination by all routes normalized to the concentration of drug C in some biological fluid:

$$CL = \text{Rate of elimination}/C \quad (2)$$

It is important to note that clearance does not indicate how much drug is being removed but, rather, the volume of biological fluid such as blood or plasma that would have to be completely freed of drug to account for the elimination. Clearance is expressed as a volume per unit of time. Clearance is usually further defined as blood clearance (CL_b), plasma clearance (CL_p), or clearance based on the concentration of unbound or free drug (CL_u), depending on the concentration measured (C_b, C_p, or C_u). (For additional discussion of clearance concepts, *see* Benet *et al.*, 1984.)

Clearance by means of various organs of elimination is additive. Elimination of drug may occur as a result of processes that occur in the kidney, liver, and other organs. Division of the rate of elimination by each organ by a concentration of drug (*e.g.*, plasma concentration) will yield the respective clearance by that organ. Added together, these separate clearances will equal total systemic clearance:

$$CL_{renal} + CL_{hepatic} + CL_{other} = CL_{systemic} \quad (3)$$

Other routes of elimination could include that in saliva or sweat, partition into the gut, and metabolism at other sites.

Total systemic clearance may be determined at steady state by using equation 1. For a single dose of a drug with complete bioavailability and first-order kinetics of elimination, total systemic clearance may be determined from mass balance and the integration of equation 2 over time.

$$CL = \text{Dose}/AUC \quad (4)$$

where AUC is the total area under the curve that describes the concentration of drug in the systemic circulation as a function of time (from zero to infinity).

Examples. In Appendix II, the plasma clearance for cephalexin is reported as 4.3 ml · min^{-1} · kg^{-1}, with 91% of the drug excreted unchanged in the urine. For a 70-kg man, the total body clearance from plasma would be 300 ml/min, with renal clearance accounting for 91% of this elimination. In other words, the kidney is able to excrete cephalexin at a rate such that approximately 273 ml of

plasma would be freed of drug per minute. Because clearance is usually assumed to remain constant in a stable patient, the total rate of elimination of cephalexin will depend on the concentration of drug in the plasma (equation 2). Propranolol is cleared at a rate of 12 ml · min^{-1} · kg^{-1} (or 840 ml/min in a 70-kg man), almost exclusively by the liver. Thus, the liver is able to remove the amount of drug contained in 840 ml of plasma per minute. Of the drugs listed in Appendix II, one of the highest values of plasma clearance is that for labetalol—1750 ml/min; this value exceeds the rate of plasma (and blood) flow to the liver, the dominant organ for elimination of this drug. However, because labetalol partitions readily into red blood cells ($C_{rbc}/C_p = 1.8$), the amount of drug delivered to the excretory organ is considerably higher than suspected from measurement of its concentration in plasma. The relationship between plasma and blood clearance at steady state is given by:

$$\frac{CL_p}{CL_b} = \frac{C_b}{C_p} = 1 + H\left(\frac{C_{rbc}}{C_p} - 1\right) \quad (5)$$

One may solve for labetalol clearance from blood by substituting the red blood cell to plasma concentration ratio and the average value for the hematocrit ($H = 0.45$). Clearance of labetalol, when measured in terms of its concentration in blood, is actually 1290 ml/min, a more reasonable value. Thus the plasma clearance may assume values that are not "physiological." A drug with an extremely low concentration in plasma that is concentrated in erythrocytes (*e.g.*, mecamylamine) can show a plasma clearance of tens of liters per minute. However, if the concentration in blood is used to define clearance, the maximal clearance possible is equal to the sum of blood flows to the various organs of elimination.

As mentioned, clearance of most drugs is constant over the range of concentration in plasma or blood that is encountered in clinical settings. This means that elimination is not saturated and the rate of elimination of drug is directly proportional to its concentration (equation 2). For drugs that exhibit saturable or dose-dependent elimination, clearance will vary with the concentration of drug, often according to the following equation:

$$\text{Total plasma clearance} = V_m/(K_m + C_p) \quad (6)$$

where K_m represents the plasma concentration at which half of the maximal rate of elimination is reached (in units of mass/volume) and V_m is equal to the maximal rate of elimination (in units of mass/time). This equation is entirely analogous to the Michaelis–Menten equation for enzyme kinetics. Design of dosage regimens for such drugs is more complex (*see* below).

A further definition of clearance is useful for understanding the effects of pathological and physiological variables on drug elimination, particularly with respect to an individual organ. The rate of elimination of a drug by an individual organ can be defined in terms of the blood flow to the organ and the concentration of drug in the blood. The rate of presentation of drug to the organ is the product of blood flow (Q) and the arterial drug concentration (C_A), and the rate of exit of drug from the organ is the product of blood flow and the venous drug concentration (C_V). The difference between these rates at steady state is the rate of drug elimination:

$$\begin{aligned}\text{Rate of elimination} &= Q \cdot C_A - Q \cdot C_V \\ &= Q(C_A - C_V)\end{aligned} \quad (7)$$

Division of equation 7 by the concentration of drug that enters the organ of elimination, C_A, yields an expression for clearance of the drug by the organ in question:

$$CL_{organ} = Q\left(\frac{C_A - C_V}{C_A}\right) = Q \cdot E \quad (8)$$

The expression $(C_A - C_V)/C_A$ in equation 8 can be referred to as the extraction ratio for the drug (E).

Hepatic Clearance. The concepts developed in equation 8 have important implications for drugs that are eliminated by the liver. Consider a drug that is efficiently removed from the blood by hepatic processes—biotransformation and/or excretion of unchanged drug into the bile. In this instance, the concentration of drug in the blood leaving the liver will be low, the extraction ratio will approach unity, and the clearance of the drug from blood will become limited by hepatic blood flow. Drugs that are cleared efficiently by the liver (*e.g.*, drugs in Appendix II with clearances greater than 6 ml · min^{-1} · kg^{-1}, such as chlorpromazine, diltiazem, imipramine, lidocaine, morphine, and propranolol) are restricted in their rate of elimination not by intrahepatic processes but by the rate at which they can be transported in the blood to hepatic sites of elimination.

Additional complexities have also been considered. For example, the equations presented above do not account for drug binding to components of blood and tissues, nor do they permit an estimation of the intrinsic ability of the liver or kidney to eliminate a drug in the absence of limitations imposed by

blood flow. Extensions of the relationships of equation 8 to include expressions for protein binding and intrinsic clearance have been proposed for a number of models of hepatic elimination (*see* Roberts *et al.*, 1988). All of these models indicate that when the capacity of the eliminating organ to metabolize the drug is large in comparison with the rate of presentation of drug, the clearance will approximate the organ blood flow. In contrast, when the metabolic capability is small in comparison to the rate of drug presentation, the clearance will be proportional to the unbound fraction of drug in blood and the intrinsic clearance. Appreciation of these concepts allows one to understand a number of possibly puzzling experimental results. For example, enzyme induction or hepatic disease may change the rate of drug metabolism in an isolated hepatic microsomal enzyme system but not change clearance in the whole animal. For a drug with a high extraction ratio, clearance is limited by blood flow, and changes in the intrinsic clearance due to enzyme induction or hepatic disease should have little effect. Similarly, for drugs with high extraction ratios, changes in protein binding due to disease or competitive binding interactions should have little effect on clearance. In contrast, changes in intrinsic clearance and protein binding will affect the clearance of drugs with low extraction ratios but changes in blood flow should have little effect.

Renal Clearance. Renal clearance of a drug results in its appearance as such in the urine; changes in the pharmacokinetic properties of drugs due to renal disease may also be explained in terms of clearance concepts. However, the complications that relate to filtration, active secretion, and reabsorption must be considered. The rate of filtration of a drug depends on the volume of fluid that is filtered in the glomerulus and the unbound concentration of drug in plasma, since drug bound to protein is not filtered. The rate of secretion of drug by the kidney will depend on the binding of drug to the proteins involved in active transport relative to that bound to plasma proteins, the degree of saturation of these carriers, the rate of transfer of the drug across the tubular membrane, and the rate of delivery of the drug to the secretory site. The influences of changes in protein binding, blood flow, and the number of functional nephrons are analogous to the examples given above for hepatic elimination.

DISTRIBUTION

Volume of Distribution. Volume is a second fundamental parameter that is useful in discussing processes of drug disposition. The volume of distribution (V) relates the amount of drug in the body to the concentration of drug (C) in the blood or plasma, depending upon the fluid measured. This volume does not necessarily refer to an identifiable physiological volume, but merely to the fluid volume that would be required to contain all of the drug in the body at the same concentration as in the blood or plasma:

$$V = \text{Amount of drug in body}/C \quad (9)$$

The plasma volume of a normal 70-kg man is 3 liters, blood volume is about 5.5 liters, extracellular fluid volume outside the plasma is 12 liters, and the volume of total body water is approximately 42 liters. However, many drugs exhibit volumes of distribution far in excess of these values. For example, if 500 μg of digoxin were in the body of a 70-kg subject, a plasma concentration of approximately 0.7 ng/ml would be observed. Dividing the amount of drug in the body by the plasma concentration yields a volume of distribution for digoxin of about 700 liters, or a value ten times greater than the total body volume of a 70-kg man. In fact, digoxin, which is relatively hydrophobic, distributes preferentially to muscle and adipose tissue and to its specific receptors, leaving a very small amount of drug in the plasma. For drugs that are extensively bound to plasma proteins but that are not bound to tissue components, the volume of distribution will approach that of the plasma volume. In contrast, certain drugs have high volumes of distribution even though most of the drug in the circulation is bound to albumin, because these drugs are also sequestered elsewhere.

The volume of distribution may vary widely depending on the pK_a of the drug, the degree of binding to plasma proteins, the partition coefficient of the drug in fat, the degree of binding to other tissues, and so forth. As might be expected, the volume of distribution for a given drug can change as a function of the patient's age, gender, disease, and body composition.

Several volume terms are commonly used to describe drug distribution, and they have been derived in a number of ways. The volume of distribution defined in equation 9 considers the body as a single homogeneous compartment (Figure 1–1). In this one-compartment model, all drug administration occurs directly into the central compartment and distribution of drug is instantaneous throughout volume (V). Clearance

of drug from this compartment occurs in a first-order fashion, as defined in equation 2; that is, the amount of drug eliminated per unit time depends on the amount (concentration) of drug in the body compartment. Figure 1–5, *A* and equation 10 describe the decline of plasma concentration with time for a drug introduced into this compartment.

$$C = (\text{Dose}/V) \cdot exp(-kt) \qquad (10)$$

where k is the rate constant for elimination of the drug from the compartment. This rate constant is inversely related to the half-life of the drug ($k = 0.693/t_{1/2}$).

For most drugs the idealized one-compartment model discussed above does not describe the entire time course of the plasma concentration. That is, certain tissue reservoirs can be distinguished from the central compartment, and the drug concentration appears to decay in a manner that can be described by multiple exponential terms (*see* Figure 1–5, *B*).

Rate of Drug Distribution. The multiple exponential decay observed for a drug that is eliminated from the body with first-order kinetics results from differences in the rates at which the drug equilibrates with tissue reservoirs. The rate of equilibration will depend upon the ratio of the perfusion of the tissue to the partition of drug into the tissue. In

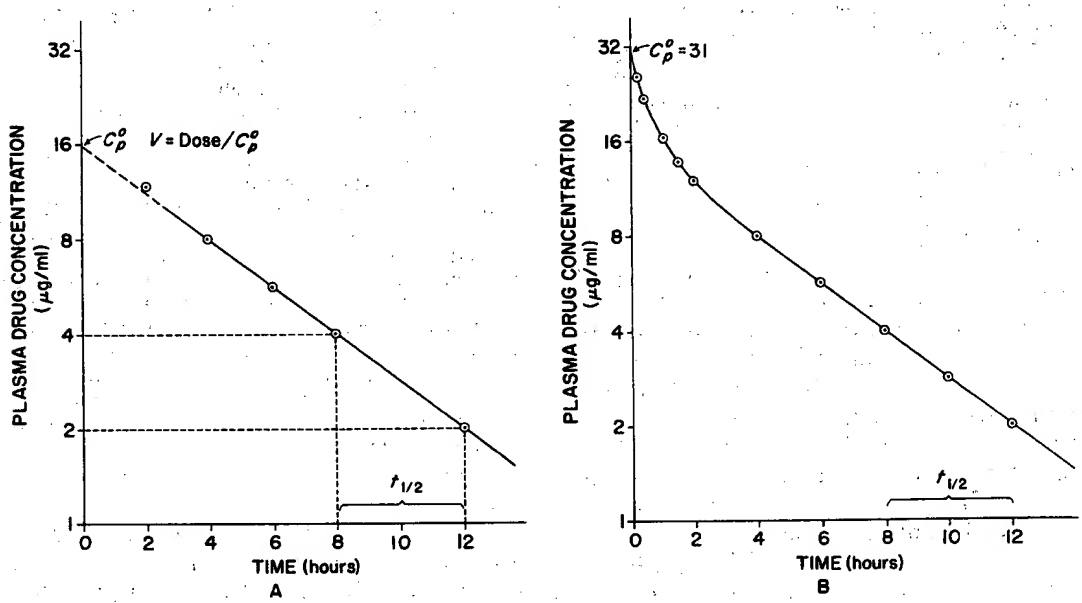

Figure 1–5. *Plasma concentration–time curves following intravenous administration of a drug (500 mg) to a 70-kg man.*

A. In this example, drug concentrations are measured in plasma 2 hours after the dose is administered. The semilogarithmic plot of plasma concentration versus time appears to indicate that the drug is eliminated from a single compartment by a first-order process (equation 10) with a half-life of 4 hours ($k = 0.693/t_{1/2} = 0.173\ hr^{-1}$). The volume of distribution (V) may be determined from the value of C_p obtained by extrapolation to $t = 0$ ($C_p^o = 16\ \mu g/ml$). Volume of distribution (equation 9) for the one-compartment model is 31.3 liters or 0.45 liter/kg ($V = \text{dose}/C_p^o$). The clearance for this drug is 92 ml/min; for a one-compartment model, $CL = k \cdot V$.

B. Sampling before 2 hours indicates that, in fact, the drug follows multiexponential kinetics. The terminal disposition half-life is 4 hours, clearance is 103 ml/min (equation 4), V_{area} is 28 liters (equation 11), and V_{ss} is 25.4 liters (equation 12). The initial or "central" distribution volume for the drug ($V_1 = \text{dose}/C_p^o$) is 16.1 liters. The example chosen indicates that multicompartment kinetics may be overlooked when sampling at early times is neglected. In this particular case, there is only a 10% error in the estimate of clearance when the multicompartment characteristics are ignored. However, for many drugs multicompartment kinetics may be observed for significant periods of time, and failure to consider the distribution phase can lead to significant errors in estimates of clearance and in predictions of the appropriate dosage.

many cases, groups of tissues with similar perfusion/partition ratios all equilibrate at essentially the same rate, such that only one apparent phase of distribution (rapid initial fall of concentration, as in Figure 1–5, *B*) is seen. It is as though the drug starts in a "central" volume, which consists of plasma and tissue reservoirs that are in rapid equilibrium with it, and distributes to a "final" volume, at which point concentrations in plasma decrease in a log-linear fashion at rate k (*see* Figure 1–5, *B*).

If the pattern or ratio of blood flows to various tissues changes within an individual or differs between individuals, rates of drug distribution to tissues will also change. However, changes in blood flow may also cause some tissues that were originally in the "central" volume to equilibrate sufficiently more slowly so as to appear only in the "final" volume. This means that central volumes will appear to vary with disease states that cause altered regional blood flow. After an intravenous bolus dose, drug concentrations in plasma may be higher in individuals with poor perfusion (*e.g.*, shock) than they would be if perfusion were better. These higher systemic concentrations may, in turn, cause higher concentrations (and greater effects) in tissues such as brain and heart whose usually high perfusion has not been reduced by the altered hemodynamic state. Thus, the effect of a drug at various sites of action can be variable, depending on perfusion of these sites.

Multicompartment Volume Terms. Two different terms have been used to describe the volume of distribution for drugs that follow multiple exponential decay. The first, designated V_{area}, is calculated as the ratio of clearance to the rate of decline of concentration during the elimination (final) phase of the logarithmic concentration versus time curve:

$$V_{area} = \frac{CL}{k} = \frac{\text{Dose}}{k \cdot AUC} \qquad (11)$$

The calculation of this parameter is straightforward, and the volume term may be determined after administration of drug by intravenous or enteral routes (where the dose used must be corrected for bioavailability). However, another multicompartment volume of distribution may be more useful, especially when the effect of disease states on pharmacokinetics is to be determined. The volume of distribution at steady state (V_{ss}) represents the volume in which a drug would appear to be distributed during steady state if the drug existed throughout that volume at the same concentration as that in the measured fluid (plasma or blood). This volume can be determined by the use of areas, as described by Benet and Galeazzi (1979):

$$V_{ss} = (\text{Dose}_{iv})(AUMC)/AUC^2 \qquad (12)$$

where $AUMC$ is the area under the first moment of the curve that describes the time course of the plasma or blood concentration, that is, the area under the curve of the product of time t and plasma or blood concentration C over the time span zero to infinity.

Although V_{area} is a convenient and easily calculated parameter, it varies when the rate constant for drug elimination changes, even when there has been no change in the distribution space. This is because the terminal rate of decline of the concentration of drug in blood or plasma depends not only on clearance but also on the rates of distribution of drug between the central and final volumes. V_{ss} does not suffer from this disadvantage (*see* Benet *et al.*, 1984).

HALF-LIFE

The half-life ($t_{1/2}$) is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%. For the simplest case, the one-compartment model (Figure 1–5, *A*), half-life may be determined readily and used to make decisions about drug dosage. However, as indicated in Figure 1–5, *B*, drug concentrations in plasma often follow a multiexponential pattern of decline; two or more half-life terms may thus be calculated.

In the past, the half-life that was usually reported corresponded to the terminal log-linear phase of elimination. However, as greater analytical sensitivity has been achieved, the lower concentrations measured appeared to yield longer and longer terminal half-lives. For example, a terminal half-life of 53 hours is observed for gentamicin (versus the 2-to-3-hour value in Appendix II), and biliary cycling is probably responsible for the 120-hour terminal value for indomethacin (as compared with the 2.4-hour half-life listed in Appendix II). The relevance of a particular half-life may be defined in terms of the fraction of the clearance and volume of distribution that is related to each half-life and whether plasma concentrations or amounts of drug in the body are best related to measures of response (*see* Benet, 1984). The single half-life values given for each drug in Appendix II are chosen to represent the most clinically relevant half-life.

Early studies of pharmacokinetic properties of drugs in disease were compromised by their reliance on half-life as the sole measure of alterations of drug disposition. Only recently has it been appreciated that half-life is a derived parameter that changes as a function of both clearance and volume of distribution. A useful approximate relationship between the clinically relevant half-life, clearance, and volume of distribution is given by:

$$t_{1/2} \cong 0.693 \cdot V/CL \qquad (13)$$

Clearance is the measure of the body's ability to eliminate a drug. However, the organs of elimination can only clear drug from the blood or plasma with which they are in direct contact. As clearance decreases, due to a disease process, for example, half-life would be expected to increase. However, this reciprocal relationship is exact only when the disease does not change the volume of distribution. For example, the half-life of diazepam increases with increasing age; however, it is not clearance that changes as a function of age, but the volume of distribution (Klotz *et al.*, 1975). Similarly, changes in protein binding of the drug may affect its clearance as well as its volume of distribution, leading to unpredictable changes in half-life as a function of disease. The half-life of tolbutamide, for example, decreases in patients with acute viral hepatitis, exactly the opposite from what one might expect. The disease appears to modify protein binding in both plasma and tissues, causing no change in volume of distribution but an increase in total clearance because higher concentrations of free drug are present (Williams *et al.*, 1977).

Although it can be a poor index of drug elimination, half-life does provide a good indication of the time required to reach steady state after a dosage regimen is initiated (*i.e.*, four half-lives to reach approximately 94% of a new steady state), the time for a drug to be removed from the body, and a means to estimate the appropriate dosing interval (*see* below).

Steady State. Equation 1 indicates that a steady-state concentration will eventually be achieved when a drug is administered at a constant rate. At this point, drug elimination (the product of clearance and concentration; equation 2) will equal the rate of drug availability. This concept also extends to intermittent dosage (*e.g.*, 250 mg of drug every 8 hours). During each interdose interval, the concentration of drug rises and falls. At steady state, the entire cycle is repeated identically in each interval. Equation 1 still applies for intermittent dosing, but it now describes the average drug concentration during an interdose interval. Steady-state dosing is illustrated in Figure 1–6.

Extent and Rate of Availability

Bioavailability. It is important to distinguish between the rate and extent of drug absorption and the amount that ultimately reaches the systemic circulation, as discussed above. The amount of the drug that reaches the systemic circulation can be expressed as a fraction of the dose F, which is often called bioavailability. Reasons for incomplete absorption have been discussed above. Also, as noted previously, if the drug is metabolized in the liver or excreted in bile, some of the active drug absorbed from the gastrointestinal tract will be inactivated by the liver before it can reach the general circulation and be distributed to its sites of action.

Knowing the extraction ratio (E) for a drug across the liver (*see* equation 8), it is possible to predict the maximum oral availability (F_{max}), assuming hepatic elimination follows first-order processes:

$$F_{max} = 1 - E = 1 - (CL_{hepatic}/Q_{hepatic}) \quad (14)$$

Thus, if the hepatic blood clearance for the drug is large relative to hepatic blood flow, the extent of availability will be low when it is given orally (*e.g.*, lidocaine). This decrease in availability is a function of the physiological site from which absorption takes place, and no modification of dosage form will improve the availability under conditions of linear kinetics.

When drugs are administered by a route that is subject to first-pass loss, the equations presented previously that contain the terms *dose* or *dosing rate* (equations 1, 4, 10, and 11) must also include the bioavailability term F such that the available dose or dosing rate is used. For example, equation 1 is modified to:

$$F \cdot \text{Dosing rate} = CL \cdot C_{ss} \quad (15)$$

Rate of Absorption. Although the rate of drug absorption does not, in general, influence the average steady-state concentration of the drug in plasma, it may still influence drug therapy. If a drug is absorbed very rapidly (*e.g.*, a dose given as an intravenous bolus) and has a small central vol-

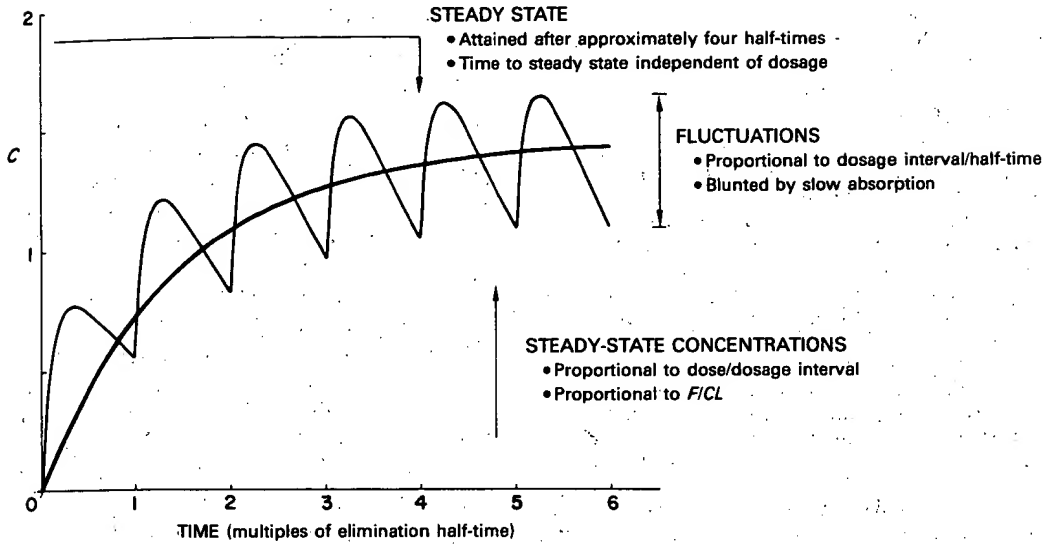

Figure 1–6. *Fundamental pharmacokinetic relationships for repeated administration of drugs.*

Light line is the pattern of drug accumulation during repeated administration of a drug at intervals equal to its elimination half-time, when drug absorption is ten times as rapid as elimination. As the relative rate of absorption increases, the concentration maxima approach 2 and the minima approach 1 during the steady state. Heavy line depicts the pattern during administration of equivalent dosage by continuous intravenous infusion. Curves are based upon the one-compartment model.

Average concentration ($\overline{C}_{ss}$) when the steady state is attained during intermittent drug administration:

$$\overline{C}_{ss} = \frac{F \cdot \text{dose}}{CL \cdot T}$$

where F = fractional bioavailability of the dose and T = dosage interval (time). By substitution of infusion rate for $F \cdot \text{dose}/T$, the formula is equivalent to equation 1 and provides the concentration maintained at steady state during continuous intravenous infusion.

ume, the concentration of drug will be high initially. It will then fall as the drug is distributed to its final (larger) volume (*see* Figure 1–5, *B*). If the same drug is absorbed more slowly (*e.g.*, by slow infusion), it will be distributed while it is being given, and peak concentrations will be lower and will occur later. A given drug may act to produce both desirable and undesirable effects at several sites in the body, and the rates of distribution of drug to these sites may not be the same. The relative intensities of these different effects of a drug may thus vary transiently when its rate of administration is changed.

NONLINEAR PHARMACOKINETICS

Nonlinearity in pharmacokinetics (*i.e.*, changes in such parameters as clearance, volume of distribution, and half-life as a function of dose or concentration of drug) is usually due to saturation of protein binding, hepatic metabolism, or active renal transport of the drug.

Saturable Protein Binding. As the molar concentration of drug increases, the unbound fraction must eventually also increase (as all binding sites become saturated). This usually occurs only when drug concentrations in plasma are in the range of tens to hundreds of micrograms per milliliter. For a drug that is metabolized by the liver with a low extraction ratio, saturation of plasma protein binding will cause both V and clearance to increase as drug concentrations increase; half-life may thus remain constant (*see* equation 13). For such a drug, C_{ss} will not increase linearly as the rate of drug administration is increased. For drugs that are cleared with high extraction ratios, C_{ss} can remain linearly proportional to the rate of drug administration. In this case, hepatic clearance would not change, and the increase in V would increase the half-time of disap-

pearance by reducing the fraction of the total drug in the body that is delivered to the liver per unit time. Most drugs fall between these two extremes, and the effects of nonlinear protein binding may be difficult to predict.

Saturable Metabolism. In this situation, the Michaelis–Menten equation (equation 6) usually describes the nonlinearity. All active processes are undoubtedly saturable, but they will appear to be linear if values of drug concentrations encountered in practice are much less than K_m. When they exceed K_m, nonlinear kinetics is observed. The major consequences of saturation of metabolism are the opposite of those for saturation of protein binding. When both conditions are present simultaneously, they may virtually cancel each others' effects, and surprisingly linear kinetics may result; this occurs over a certain range of concentrations for salicylic acid.

Saturable metabolism causes first-pass metabolism to be less than expected (higher F), and there is a greater fractional increase in C_{ss} than the corresponding fractional increase in the rate of drug administration. The latter can be seen most easily by substituting equation 6 into equation 1 and solving for the steady-state concentration:

$$C_{ss} = \frac{\text{Dosing rate} \cdot K_m}{V_m - \text{Dosing rate}} \qquad (16)$$

As the dosing rate approaches the maximal elimination rate (V_m), the denominator of equation 16 approaches zero and C_{ss} increases disproportionately. Fortunately, saturation of metabolism should have no effect on the volume of distribution; thus, as clearance decreases, the apparent half-life for elimination increases and the approach to the (disproportionate) new steady state is slow. However, the concept of "four half-lives to steady state" is not applicable for drugs with nonlinear metabolism in the usual range of clinical concentrations.

Phenytoin provides an example of a drug for which metabolism becomes saturated in the therapeutic range of concentrations (*see* Appendix II). K_m is typically near the lower end of the therapeutic range (K_m = 5 to 10 mg per liter). For some individuals, especially children, K_m may be as low as 1 mg per liter. If, for such an individual, the target concentration is 15 mg per liter and this is attained at a dosing rate of 300 mg per day, then, from equation 16, V_m equals 320 mg per day. For such a patient, a dose 10% less than optimal (*i.e.*, 270 mg per day) will produce a C_{ss} of 5 mg per liter, well below the desired value. In contrast, a dose 10% greater than optimal (330 mg per day) will exceed metabolic capacity (by 10 mg per day) and cause a long and slow but unending climb in concentration until toxicity occurs. Dosage cannot be controlled so precisely (less than 10% error). Therefore, for those patients in whom the target concentration for phenytoin is more than tenfold greater than the K_m, alternating inefficacious therapy and toxicity is almost unavoidable.

Design and Optimization of Dosage Regimens

When long-term therapy is initiated, a pharmacodynamic question must be asked: What degree of drug effect is desired and achievable? If some effect of the drug is easily measured (*e.g.*, blood pressure), it can be used to guide dosage, and a trial-and-error approach to optimal dosage is both practical and sensible. Even in this ideal case, certain quantitative issues arise, such as how often to change dosage and by how much. These can usually be settled with simple rules of thumb based on the principles discussed (*e.g.*, change dosage by no more than 50% and no more often than every three to four half-lives). Alternatively, some drugs have very little dose-related toxicity, and maximum efficacy is usually desired. For these drugs, doses well in excess of the average required will both ensure efficacy (if this is possible) and prolong drug action. Such a "maximal dose" strategy is typically used for penicillins and most β-adrenergic blocking agents.

Target Level. For some drugs, the effects are difficult to measure (or the drug is given for prophylaxis), toxicity and lack of efficacy are both potential dangers, and/or the therapeutic index is narrow. In these circumstances doses must be titrated carefully, and a target-level strategy is reasonable. A desired (target) steady-state concentration of the drug (usually in plasma) is chosen, and a dosage is computed that is expected to achieve this value. Drug concentrations are subsequently measured, and dosage is adjusted if necessary to approximate the target more closely (*see also* Chapter 4).

To apply the target-level strategy, the therapeutic objective must be defined in terms of a desirable range for the C_{ss}, often called the therapeutic range. For drugs for which this can be done, such as theophylline and digoxin, the lower limit of the therapeutic range appears to be approximately equal to the drug concentration that produces about half of the greatest possible therapeutic effect. The upper limit of the therapeutic range (for drugs with such a limit) is fixed by toxicity, not by efficacy.

In general, the upper limit of the therapeutic range is such that no more than 5 to 10% of patients will experience a toxic effect. For some drugs, this may mean that the upper limit of the range is no more than twice the lower limit. Of course, these figures can be highly variable, and some patients may benefit greatly from drug concentrations that exceed the therapeutic range while others may suffer significant toxicity at much lower values. Barring more specific information, however, the target is usually chosen as the center of the therapeutic range.

Maintenance Dose. In most clinical situations, drugs are administered in a series of repetitive doses or as a continuous infusion in order to maintain a steady-state concentration of drug in plasma within a given therapeutic range. Thus, calculation of the appropriate maintenance dosage is a primary goal. To maintain the chosen steady-state or target concentration, the rate of drug administration is adjusted such that the rate of input equals the rate of loss. This relationship was defined previously in equations 1 and 15 and is expressed here in terms of the desired target concentration:

$$\text{Dosing rate} = \text{Target} \cdot CL/F \tag{17}$$

If the clinician chooses the desired concentration of drug in plasma and knows the clearance and availability for that drug in a particular patient, the appropriate dose and dosing interval can be calculated.

Example. A steady-state plasma concentration of theophylline of 15 mg per liter is desired to relieve acute bronchial asthma in a 68-kg patient. If the patient does not smoke and is otherwise normal except for the asthmatic condition, one can use the mean clearance given in Appendix II, that is, 0.65 ml · min^{-1} · kg^{-1}. Because the drug is to be given as an intravenous infusion, $F = 1$:

$$\begin{aligned}\text{Dosing rate} &= \text{Target} \cdot CL/F \\ &= 15\ \mu g/ml \cdot 0.65\ ml \cdot min^{-1} \cdot kg^{-1} \\ &= 9.75\ \mu g \cdot min^{-1} \cdot kg^{-1} \\ &= 40\ mg/hr \text{ for a 68-kg patient}\end{aligned}$$

Since almost all intravenous preparations of theophylline are available as the ethylenediamine salt (aminophylline), which contains 85% theophylline, the infusion rate will be 47 mg per hour of aminophylline [(40 mg per hour)/(0.85)].

Dosing Interval for Intermittent Dosage. In general, marked fluctuations in drug concentrations between doses are not beneficial. If absorption and distribution were instantaneous, fluctuation of drug concentrations between doses would be governed entirely by the drug's elimination half-life. If the dosing interval (T) was chosen to be equal to the half-life, then the total fluctuation would be twofold; this is usually a tolerable variation.

Pharmacodynamic considerations modify this. If a drug is relatively nontoxic, such that concentrations many times that necessary for therapy can easily be tolerated, the maximal dose strategy can be used and the dosing interval can be much longer than the elimination half-life (for convenience). The half-life of penicillin G is less than 1 hour, but it is often given in very large doses every 6 or 12 hours.

For some drugs with a narrow therapeutic range, it may be important to estimate the maximal and minimal concentrations that will occur for a particular dosing interval. The minimal steady-state concentration $C_{ss,min}$ may be reasonably determined by the use of equation 18:

$$C_{ss,min} = \frac{F \cdot \text{dose}/V_{ss}}{1 - exp(-kT)} \cdot exp(-kT) \tag{18}$$

where k equals 0.693 divided by the clinically relevant plasma half-life and T is the dosing interval. The term $exp(-kT)$ is, in fact, the fraction of the last dose (corrected for bioavailability) that remains in the body at the end of a dosing interval.

For drugs that follow multiexponential kinetics and that are administered orally, the estimation of the maximal steady-state concentration $C_{ss,max}$ involves a complicated set of exponential constants for distribution and absorption. If these terms are ignored for multiple oral dosing, one may easily predict a maximal steady-state concentration by omitting the $exp(-kT)$ term in the numerator of equation 18 (*see* equation 19, below). Because of the approximation, the predicted maximal concentration from equation 19 will be greater than that actually observed.

Example. When the acute asthmatic attack in the patient discussed above is relieved, the clinician might want to maintain the plasma concentration of theophylline at 15 mg per liter, with oral dosage at intervals of 6, 8, or 12 hours. The correct rate of drug administration, independent of consideration of the dosing interval, is 40 mg per hour for this patient, as calculated above, since the availability of theophylline from an oral dose is 100%. Thus, the appropriate intermittent doses would be 240 mg every 6 hours, 320 mg every 8 hours, or 480 mg every 12 hours. All of these regimens would yield the same average concentration of 15 mg per liter, but different maximal and minimal concentrations would obtain. For a 12-hour dosing interval, the following maximal and minimal concentrations would be predicted:

$$C_{ss,max} = \frac{F \cdot \text{dose}/V_{ss}}{1 - exp(-kT)} = \frac{480 \text{ mg}/34 \text{ liters}}{0.65} = 22 \text{ mg/liter} \quad (19)$$

$$C_{ss,min} = C_{ss,max} \cdot exp(-kT) = (21.7 \text{ mg/liter}) \cdot (0.35) = 7.6 \text{ mg/liter} \quad (20)$$

The calculations in equations 19 and 20 were performed assuming oral doses of 480 mg every 12 hours of a drug with a half-life of 8 hours (k = 0.693/8 hr = 0.0866 hr^{-1}), a volume of distribution of 0.5 liter/kg (V_{ss} = 34 liters for a 68-kg patient), and an oral availability of 1. Since the predicted minimal concentration, 7.6 mg per liter, falls below the suggested effective concentration and the predicted maximal concentration is above that suggested to avoid toxicity (*see* Appendix II), the choice of a 12-hour dosing interval is probably inappropriate. A more appropriate choice would be 320 mg every 8 hours or 240 mg every 6 hours; for T = 6 hr, $C_{ss,max}$ = 17 mg per liter; $C_{ss,min}$ = 10 mg per liter. Of course the clinician must balance the problem of compliance with regimens that involve frequent dosage against the problem of periods when the patient may be subjected to concentrations of the drug that could be too high or too low.

Loading Dose. The "loading dose" is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly. The appropriate magnitude for the loading dose is:

$$\text{Loading dose} = \text{Target } C_p \cdot V_{ss}/F \quad (21)$$

A loading dose may be desirable if the time required to attain steady state by the administration of drug at a constant rate (four elimination half-lives) is long relative to the temporal demands of the condition being treated. For example, the half-life of lidocaine is usually more than 1 hour. Arrhythmias encountered after myocardial infarction may obviously be life threatening, and one cannot wait 4 to 6 hours to achieve a therapeutic concentration of lidocaine by infusion of the drug at the rate required to maintain this concentration. Hence, use of a loading dose of lidocaine in the coronary care unit is standard.

The use of a loading dose also has significant disadvantages. First, the particularly sensitive individual may be exposed abruptly to a toxic concentration of a drug. Moreover, if the drug involved has a long half-life, it will take a long time for the concentration to fall if the level achieved was excessive. Loading doses tend to be large, and they are often given parenterally and rapidly; this can be particularly dangerous if toxic effects occur as a result of actions of the drug at sites that are in rapid equilibrium with plasma.

Individualizing Dosage. To design a rational dosage regimen, the clinician must know F, CL, V_{ss}, and $t_{1/2}$, and have some knowledge about rates of absorption and distribution of the drug. Moreover, one must judge what variations in these parameters might be expected in a particular patient. Usual values for the important parameters and appropriate adjustments that may be necessitated by disease or other factors are presented in Appendix II. There is, however, unpredictable variation between normal individuals; for many drugs, one standard deviation in the values observed for F, CL, and V_{ss} is about 20%, 50%, and 30%, respectively. This means that 95% of the time the C_{ss} that is achieved will be between 35% and 270% of the target; this is an unacceptably wide range for a drug with a low therapeutic index. If values of C_p are measured, one can estimate values of F, CL, and V_{ss} directly, and this permits more precise adjustment of a dosage regimen. Such measurement and adjustment are appropriate for many drugs with low therapeutic indices (*e.g.*, cardiac glycosides, antiarrhythmic agents, anticonvulsants, theophylline, and others).

Therapeutic Drug Monitoring

The major use of measured concentrations of drugs (at steady state) is to refine the estimate of CL/F for the patient being treated (using equation 15 as rearranged below):

$$CL/F \text{ (patient)} = \text{Dosing rate}/C_{ss} \text{ (measured)} \quad (22)$$

The new estimate of CL/F can be used in equation 17 to adjust the maintenance dose to achieve the desired target concentration.

Certain practical details and pitfalls related to therapeutic drug monitoring should be kept in mind. The first of these concerns the time of sam-

pling for measurement of the drug concentration. If intermittent dosing is used, when during a dosing interval should samples be taken? It is necessary to distinguish between two possible uses of measured drug concentrations in order to understand the possible answers. A concentration of drug measured in a sample taken at virtually any time during the dosing interval will provide information that may aid in the assessment of drug toxicity. This is one type of therapeutic drug monitoring. It should be stressed, however, that such use of a measured concentration of drug is fraught with difficulties because of interindividual variability in sensitivity to the drug. When there is a question of toxicity, the drug concentration can be no more than just one of many items that serve to inform the clinician.

Changes in the effects of drugs may be delayed relative to changes in plasma concentration because of a slow rate of distribution or pharmacodynamic factors. Concentrations of digoxin, for example, regularly exceed 2 ng/ml (a potentially toxic value) shortly after an oral dose, yet these peak concentrations do not cause toxicity; indeed, they occur well before peak effects. Thus, concentrations of drugs in samples obtained shortly after administration can be uninformative or even misleading.

When concentrations of drugs are used for purposes of adjusting dosage regimens, samples obtained shortly after administration of a dose are almost invariably misleading. The point of sampling during supposed steady state is to modify one's estimate of CL/F and thus one's choice of dosage. Early postabsorptive concentrations do not reflect clearance; they are determined primarily by the rate of absorption, the central (rather than the steady-state) volume of distribution, and the rate of distribution, all of which are pharmacokinetic features of virtually no relevance in choosing the long-term maintenance dosage. When the goal of measurement is adjustment of dosage, the sample should be taken well after the previous dose—as a rule of thumb just before the next planned dose, when the concentration is at its minimum. There is an exception to this approach: some drugs are nearly completely eliminated between doses and act only during the initial portion of each dosing interval. If, for such drugs, it is questionable whether efficacious concentrations are being achieved, a sample taken shortly after a dose may be helpful. Yet, if another concern is that low clearance (as in renal failure) may cause accumulation of drug, concentrations measured just before the next dose will reveal such accumulation and are considerably more useful for this purpose than is knowledge of the maximal concentration. For such drugs, determination of both maximal and minimal concentrations is thus recommended.

A second important aspect of the timing of sampling is its relationship to the beginning of the maintenance dosage regimen. When constant dosage is given, steady state is reached only after four half-lives have passed. If a sample is obtained too soon after dosage is begun, it will not accurately reflect clearance. Yet, for toxic drugs, if one waits until steady state is ensured, the damage may have been done. Some simple guidelines can be offered. When it is important to maintain careful control of concentrations, one may take the first sample after two half-lives (as calculated and expected for the patient), assuming no loading dose has been given. If the concentration already exceeds 90% of the eventual expected mean steady-state concentration, the dosage rate should be halved, another sample obtained in another two (supposed) half-lives, and the dosage halved again if this sample exceeds the target. If the first concentration is not too high, one proceeds with the initial rate of dosage; even if the concentration is lower than expected, one can usually await the attainment of steady state in another two estimated half-lives and then proceed to adjust dosage as described above.

If dosage is intermittent, there is a third concern with the time at which samples are obtained for determination of drug concentrations. If the sample has been obtained just prior to the next dose, as recommended, concentration will be a minimal value, not the mean. However, as discussed above, the estimated mean concentration may be calculated by using equation 15.

If a drug follows first-order kinetics, the average, minimum, and maximum concentrations at steady state are linearly related to dose and dosing rate (*see* equations 15, 18, and 19). Therefore, the ratio between the measured and the desired concentrations can be used to adjust the dose:

$$\frac{C_{ss}(\text{measured})}{C_{ss}(\text{desired})} = \frac{\text{Dose(previous)}}{\text{Dose(new)}} \tag{23}$$

Finally, for some drugs that are particularly difficult to manage, computer programs may be useful for the design of dosage regimens. Such programs, which take into account measured drug concentrations and individual factors such as those listed in Appendix II, are becoming increasingly available (see Sheiner *et al.*, 1972; Vozeh and Steimer, 1985).

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APPENDIX D

Transclean Corp. v. Bridgewood Serv.,
290 F.3d 1364 (Fed. Cir. 2002)

possible."). Thus, for example, in a case arising under the WPA where the government employee makes non-frivolous allegations that he was terminated in retaliation for making protected disclosures, an administrative judge could properly hold an initial hearing limited to the question of whether the employee would have been properly terminated absent the disclosures, such as where the employee's attendance record was clearly unsatisfactory. If after such a limited merits hearing the Board concluded that the employee would have been properly terminated absent the protected disclosures, the employee's claim could be rejected on the merits, subject to right of appeal to the full Board and to this court. This authority is akin to that granted district court judges by Federal Rule of Civil Procedure 16(c)(14), which allows district court judges to govern the order of proof presented at trial, and to allow separate trials of particular issues.[5]

CONCLUSION

[11] We reiterate that non-frivolous jurisdictional allegations supported by affidavits or other evidence confer Board jurisdiction. The truth of such allegations is tested in a hearing in which appellant must prove the allegations by preponderant evidence. These hearings are not "jurisdictional" hearings—they are hearings on the merits. Because we find that appellant did not waive his right to a hearing on the merits, we vacate and remand for further proceedings not inconsistent with this opinion. We do not reach the question whether the Board's finding of involuntariness was supported by substantial evidence.

COSTS

No costs.

VACATED AND REMANDED.

TRANSCLEAN CORPORATION, James P. Viken, Jon A. Lang, and Donald E. Johnson, Plaintiffs–Appellants,

v.

BRIDGEWOOD SERVICES, INC., Defendant/Cross–Appellant.

Nos. 01–1268, 01–1269.

United States Court of Appeals, Federal Circuit.

Decided: May 21, 2002.

Rehearing Denied: July 2, 2002.

Assignee of patent for automat transmission fluid changing device sue competitor for patent infringement, trad mark infringement, and false advertisin The United States District Court for tl District of Minnesota, Raymond L. Eric son, United States Magistrate Judge, e tered judgment in favor of competitor trademark infringement claim, F.Supp.2d 1045, entered judgment in fav of assignee on patent infringement a false advertising claims, but denied its m tion for enhanced damages and attorn fees, 134 F.Supp.2d 1049. Both parties a pealed. The Court of Appeals, Lourie, C cuit Judge, held that: (1) patent was

5. Rule 16(c)(14) states in pertinent part:

> At any conference under this rule consideration may be given, and the court may take appropriate action, with respect to ... an order directing a party or parties to present evidence early in the trial with respect to a manageable issue that could, on the dence, be the basis for a judgment a matter of law under Rule 50(a) or a ju ment on partial pretrial findings under R 52(c).

Fed.R.Civ.P. 16(c)(14).

anticipated by two prior art patents; (2) precluding competitor from arguing noninfringement as discovery sanction was not abuse of discretion; (3) assignee was not entitled to reasonable royalty based upon competitor's proceeds from sale of its business; (4) award of enhanced damages or attorney fees was not warranted; and (5) assignee did not sufficiently use its unregistered marks in commerce to support infringement claim.

Affirmed in part and vacated in part.

Clevenger, Circuit Judge, filed opinion dissenting in part.

1. Patents ⇐65, 72(1)

Determination that a patent is invalid as being anticipated requires a finding that each and every limitation is found either expressly or inherently in a single prior art reference; to anticipate, the reference must also enable one of skill in the art to make and use the claimed invention. 35 U.S.C.A. § 102.

2. Patents ⇐112.5

Because a patent issued by the Patent and Trademark Office (PTO) is presumed to be valid, evidentiary burden to show facts supporting a conclusion of invalidity is clear and convincing evidence. 35 U.S.C.A. § 282.

3. Patents ⇐226.6

Determination of patent infringement requires a two-step analysis: first, the court determines the scope and meaning of the patent claims asserted; second, the properly construed claims are compared to the allegedly infringing device.

4. Patents ⇐314(5), 324.5

Claim construction in patent infringement case is an issue of law that Court of Appeals reviews de novo.

5. Patents ⇐226.6, 314(5)

Comparison of patent claim to accused device requires a determination that every claim limitation or its equivalent be found in the accused device; those determinations are questions of fact.

6. Patents ⇐319(1)

Choice of methodology for calculating damages is within the discretion of the district court in patent infringement case.

7. Patents ⇐312(1.7), 324.55(1)

Patent owner bears burden of proving by preponderance of the evidence the quantum of damages, an issue of fact for which Court of Appeals reviews the jury's decision for substantial evidence.

8. Courts ⇐96(5, 7)

A decision to sanction a litigant for discovery violations is one that is not unique to patent law, and Court of Appeals for the Federal Circuit therefore applies regional circuit law to that issue. Fed. Rules Civ.Proc.Rule 37, 28 U.S.C.A.

9. Patents ⇐101(4)

Phrase "equalizing the fluid flow" in patent for automatic transmission fluid changing apparatus referred to a rate, not just a volume; specification referred to equalization of flow rates, and patent described problems that could occur in prior art when input flow rate of added fluid did not match the output flow rate of used fluid.

10. Patents ⇐65

To anticipate a patent claim reciting a means-plus-function limitation, the anticipatory reference must disclose the recited function identically. 35 U.S.C.A. § 112.

11. Patents ⇐66(1.9)

Patent for automatic transmission fluid changing apparatus which contained "means for equalizing fluid flow" means-plus-function limitation was not anticipated by two prior art patents; prior art patents disclosed equalization of fluid amount, but

not necessarily fluid flow rates. 35 U.S.C.A. § 112.

12. Patents ⇐65

Anticipation of patent by inherent disclosure is appropriate only when reference discloses prior art that must necessarily include the unstated limitation. 35 U.S.C.A. § 102.

13. Patents ⇐292.1(4)

Precluding assignee's competitor from arguing noninfringement as discovery sanction for competitor's failure to answer interrogatory seeking its bases for arguing noninfringement was not abuse of discretion in action for infringement of patent for automatic transmission fluid changing apparatus. Fed.Rules Civ.Proc.Rule 37, 28 U.S.C.A.

14. Patents ⇐101(2)

Phrase "exhibiting resilient characteristics" in patent for automatic transmission fluid changing apparatus meant "retuning to an original shape after being deformed" or "returning to its original position after being compressed."

15. Patents ⇐318(4.1)

Patent assignee was not entitled to reasonable royalty based upon infringer's proceeds from sale of its business, although infringer's sole source of revenue was infringing product; portions of sales price consisting of goodwill was not sale of infringing goods that could form base for determination of a reasonable royalty.

16. Patents ⇐319(3)

Determination that patent assignee's competitor had willfully infringed patent for automatic transmission fluid changing apparatus did not require award of enhanced damages in infringement action. 35 U.S.C.A. § 284.

17. Patents ⇐319(3)

Enhancement of damages in patent infringement case involves fact-finder determining that the infringer engaged in culpable conduct and the court exercising its discretion to determine whether and to what extent to enhance the damages. 35 U.S.C.A. § 284.

18. Patents ⇐325.11(2.1)

Determination that enhanced damages were not warranted despite willful patent infringement by patent assignee's competitor supported implicit conclusion that case was not "exceptional," within meaning of patent attorney fee statute. 35 U.S.C.A. § 285.

See publication Words and Phrases for other judicial constructions and definitions.

19. Patents ⇐325.11(5)

Generally, district court must normally explain why it decides that a case is not exceptional under patent attorney fee statute when a factual finding of willful infringement has been established and, if exceptional, why it decides not to award attorney fees. 35 U.S.C.A. § 285.

20. Trade Regulation ⇐862

Purpose of Minnesota's private attorney general statute is to encourage private parties to police unlawful trade practices affecting the public interest. M.S.A. § 8.31.

21. Attorney and Client ⇐92

Patent assignee was not entitled to award of attorney fees under Minnesota's private attorney general statute for its successful claim that competitor engaged in false advertising of its automatic transmission fluid changing product; assignee's own use of arguably false advertising and tolerance of same advertising by its licensee erased any public benefit from its successful action against competitor. M.S.A. § 8.31.

22. Trade Regulation ⇐67

Trademark holder's use of unregistered trademarks "total fluid exchange"

and "total fluid x-change" on its automatic transmission fluid change products and its documents was insufficient use of the marks in commerce to support trademark infringement claim; use of marks on documents did not satisfy usage requirement, since marks could be affixed to goods themselves, and marks were used on products in purely descriptive manner, rather than as a source identifier. Lanham Trade–Mark Act, § 43(a)(1), 15 U.S.C.A. § 1125(a)(1).

23. Trade Regulation ⇐66.1

Use of unregistered mark on documents does not satisfy usage requirement of trademark infringement claim when the mark can be affixed to the goods themselves. Lanham Trade–Mark Act, § 43(a)(1), 15 U.S.C.A. § 1125(a)(1).

Alan M. Anderson, Fulbright & Jaworski L.L.P., of Minneapolis, MN, argued for plaintiffs-appellants. With him on the brief was Christopher K. Larus.

Warren E. Olsen, Fitzpatrick, Cella, Harper & Scinto, of Washington, DC, argued for defendant-cross appellant. With him on the brief were Brian L. Klock and Stephen E. Belisle.

Before NEWMAN, LOURIE, and CLEVENGER, Circuit Judges.

LOURIE, Circuit Judge.

Transclean Corporation, James P. Viken, Jon A. Lang, and Donald E. Johnson (collectively "Transclean") appeal from a judgment of the United States District Court for the District of Minnesota (1) reversing entry of a portion of a jury's damages award for infringement of Transclean's U.S. Patent 5,318,080, *Transclean Corp. v. Bridgewood Serv., Inc.*, No. 97–2298, slip op. at 28 (D.Minn. Jan. 8, 2001) ("*Damages Opinion*"); (2) denying its motion for enhanced damages under 35 U.S.C. § 284, *id.* at 66, as well as attorney fees under 35 U.S.C. § 285 and Minn.Stat. § 8.31, *Transclean Corp. v. Bridgewood Servs., Inc.*, 134 F.Supp.2d 1049, 1061 (D.Minn.2001) ("*Attorney Fees Opinion*"); and (3) granting summary judgment of noninfringement on its claim of trademark infringement, *Transclean Corp. v. Bridgewood Serv., Inc.*, 77 F.Supp.2d 1045, 1094–95 (D.Minn.1999) ("*Summary Judgment Opinion*"). Bridgewood cross-appeals from the court's grant of summary judgment that the '080 patent is not invalid for anticipation and that Bridgewood infringed claims 1–4 and 12. *Id.* at 1063, 1081, 1083. Bridgewood also cross-appeals from the court's denial of its motion for summary judgment of noninfringement of claim 13. *Id.* at 1087. For the reasons set forth below, we affirm-in-part and vacate-in-part.

BACKGROUND

Transclean is the assignee of the '080 patent, which is directed to an automatic transmission fluid changing apparatus. The fluid circulates from an automobile's automatic transmission case to a radiator and back via circulation lines. '080 patent at col. 1, ll. 6–12. The invention of the patent is designed to tap into a fluid circulation line and become part of the circulation system for the duration of the fluid changing procedure. *Id.* at col. 3, ll. 8–19. In that configuration, the invention collects used fluid as it circulates around and into the machine, while supplying new fluid into the circulation system. *Id.* Prior to the invention, such machines were not capable of matching the supply rate of new fluid to the outflow rate of used fluid. *Id.* at col. 2, ll. 56–68. As a result, one of two problems was likely to occur. First, if the supply rate was less than the outflow rate, the transmission could become starved of fluid, which could lead to excessive heating and

damage to the transmission. *Id.* Second, if the supply rate exceeded the outflow rate, a buildup of internal fluid pressure could stress and damage seals in the transmission. *Id.* The invention aimed to solve these problems by balancing the supply rate to the outflow rate. *Id.* at col. 3, ll. 8–19. Claim 1, the only independent claim, reads as follows:

> 1. In a fluid replacing apparatus for an automatic transmission an improvement having fluid circulation inlet and outlet ports comprising:
>
> a fluid receiver adapted to be connected to the fluid circulation output port on said automatic transmission;
>
> a source of fresh transmission fluid adapted to be connected to the fluid circulation inlet port on said automatic transmission so that fluid circulates therethrough; and
>
> *means* connected to said fluid receiver and said source of fresh fluid, *for equalizing the fluid flow into said fluid receiver and out of said source of fluid.*

Id. at col. 8, ll. 10–23 (emphases added).

As can be seen, the claims recite a "means . . . for equalizing the fluid flow" in the manner authorized by 35 U.S.C. § 112, ¶ 6. The specification discloses several structures corresponding to the claimed "means." According to one structure, the fluid receiver and source of fresh transmission fluid are segregated portions of the same tank, and the means for equalizing is a flexible diaphragm that defines the boundary dividing the tank into two segregated portions. *Id.* at figure 3. A structure with those characteristics is the subject of claim 13, which reads as follows:

> 13. The apparatus of claim 1 in which the means for equalizing the flow is comprised of means disposed intermediate the fluid receiver and source, said means *exhibiting resilient characteristics* for exerting a force, related to the pressure existing in the fluid circulation circuit of said transmission and said receiver, upon the fluid in said source.

Id. at col. 8, ll. 55–61 (emphasis added). Another structure corresponding to the means for equalizing in claim 1 is a pair of tanks, one for used fluid and one for fresh fluid charged by pressurized air. *Id.* at figs. 4,6.

Bridgewood is a competing distributor of transmission service equipment to automobile service businesses. Bridgewood's accused device is the embodiment described in its own U.S. Patent 5,522,474. Briefly, Bridgewood's device consists of a reservoir divided into two chambers by a free floating piston. '474 patent, abstract. The reservoir above the piston is initially filled with fresh fluid, and the reservoir below the piston is initially empty and compressed. *Id.* Extending from each chamber is a line for connection to an automobile's automatic transmission fluid circulation system at a point where a technician breaks the fluid circuit. *Id.* Thereafter, operation of the transmission pump sends used fluid into the bottom chamber, thereby forcing the piston to expel fresh fluid from the top chamber into the transmission's fluid circulation system. *Id.* When the technician can see fresh fluid being pumped into the bottom chamber, the procedure is halted, as the fluid has been essentially completely replaced, *id.*, even though not all of the used fluid could possibly be expelled, *Attorney Fees Opinion* at 1056.

Bridgewood is no longer in business, having sold all of its assets, including goodwill, to Century Manufacturing Company for a total of $7,744,000, which was $6,522,000 above and beyond the book value of Bridgewood's tangible net worth. Century subsequently took a license under the '080 patent from Transclean, agreeing to a royalty rate of nine percent.

Transclean sued Bridgewood for infringement of the '080 patent and its TOTAL FLUID EXCHANGE and TOTAL FLUID X CHANGE trademarks, as well as false advertising by Bridgewood's promotional claims that its device replaced "100%" or "every drop" of fluid. Before trial, both parties filed motions for partial summary judgment, Transclean seeking summary judgment on the issues of patent infringement and validity, and Bridgewood seeking summary judgment of noninfringement of claim 13 as well as Transclean's trademarks. The court granted all of those motions except that relating to claim 13. More specifically, the court granted summary judgment that the '080 patent was not anticipated by either U.S. Patent 3,513,941, issued to N.J. Becnel, or Japanese Patent 2–72299. *Summary Judgment Opinion* at 1081. Furthermore, the court granted Transclean's motion for summary judgment that Bridgewood infringed claims 1–4 and 12 of the '080 patent, after precluding Bridgewood from arguing noninfringement of those claims as a sanction for Bridgewood's failure to answer an interrogatory seeking its bases for arguing noninfringement. *Id.* at 1062–63. Finally, the court granted Bridgewood's motion that Bridgewood had not infringed Transclean's trademarks. *Id.* at 1094–95.

The case was then tried to a jury, which found that Bridgewood willfully infringed claim 13 and engaged in false advertising. The jury awarded Transclean three types of damages for the patent infringement. *Damages Opinion* at 3. The first was a reasonable royalty based on Bridgewood's sales of infringing devices; the second was additional damages for the infringement; and the third was a reasonable royalty based on Bridgewood's sale of its business. *Id.*

In a post-trial motion, Bridgewood sought to overturn the jury's damages awards. The court partly agreed and held that as a matter of law Transclean was not entitled to more than $1,874,500 for patent infringement. *Id.* at 65–66. Transclean also filed a post-trial motion seeking enhanced damages and attorney fees pursuant to 35 U.S.C. §§ 284 and 285 in light of the jury's finding of willful infringement, but the court denied both requests. *Id.* at 66. Additionally, Transclean filed a post-trial motion pursuant to Minnesota's private attorney general statute, Minn.Stat. § 8.31, seeking attorney fees it incurred in pursuing the false advertising claim, but the court denied that request as well. *Id.*

Transclean appeals and Bridgewood cross-appeals from the decisions of the district court. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

We review a district court's grant of summary judgment *de novo*, reapplying the same standard used by the district court. *Ethicon Endo–Surgery, Inc. v. U.S. Surgical Corp.*, 149 F.3d 1309, 1315, 47 USPQ2d 1272, 1275 (Fed.Cir.1998). Summary judgment is appropriate "if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed. R.Civ.P. 56(c). "The evidence of the nonmovant is to be believed, and all justifiable inferences are to be drawn in his favor." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986). When both parties move for summary judgment, the court must evaluate each motion on its own merits, resolving all reasonable inferences against the party whose motion is under consideration. *McKay v. United States*, 199 F.3d 1376, 1380 (Fed.Cir.1999).

We review a district court's grant of judgment as a matter of law ("JMOL") *de novo*, reapplying the JMOL standard used by the district court. *Sextant Avionique, S.A. v. Analog Devices, Inc.*, 172 F.3d 817, 824, 49 USPQ2d 1865, 1869 (Fed.Cir.1999). JMOL is appropriate when "a party has been fully heard on an issue and there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue." Fed.R.Civ.P. 50(a)(1). To prevail, an appellant "must show that the jury's findings, presumed or express, are not supported by substantial evidence or, if they were, that the legal conclusion(s) implied from the jury's verdict cannot in law be supported by those findings." *Perkin–Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 893, 221 USPQ 669, 673 (Fed. Cir.1984) (citation omitted).

[1, 2] A determination that a patent is invalid as being anticipated under 35 U.S.C. § 102 requires a finding that "each and every limitation is found either expressly or inherently in a single prior art reference." *Celeritas Techs. Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1360, 47 USPQ2d 1516, 1522 (Fed.Cir.1998). To anticipate, the reference must also enable one of skill in the art to make and use the claimed invention. *In re Donohue*, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir.1985). Because a patent issued by the U.S. Patent and Trademark Office is presumed to be valid, 35 U.S.C. § 282 (1994), the evidentiary burden to show facts supporting a conclusion of invalidity is clear and convincing evidence, *WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1355, 51 USPQ2d 1385, 1396–97 (Fed.Cir. 1999).

[3–5] A determination of infringement requires a two-step analysis. "First, the court determines the scope and meaning of the patent claims asserted ... [Second,] the properly construed claims are compared to the allegedly infringing device." *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454, 46 USPQ2d 1169, 1172 (Fed. Cir.1998) (en banc) (citations omitted). Step one, claim construction, is an issue of law, *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 970–71, 34 USPQ2d 1321, 1322 (Fed.Cir.1995) (en banc), *aff'd*, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996), that we review *de novo*, *Cybor*, 138 F.3d at 1456, 46 USPQ2d at 1172 (Fed.Cir.1998). Step two, comparison of the claim to the accused device, requires a determination that every claim limitation or its equivalent be found in the accused device. *Warner–Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29, 117 S.Ct. 1040, 137 L.Ed.2d 146 (1997). Those determinations are questions of fact. *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353, 48 USPQ2d 1674, 1676 (Fed.Cir.1998).

[6, 7] The choice of methodology for calculating damages is within the discretion of the district court. *SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 926 F.2d 1161, 1164, 17 USPQ2d 1922, 1925 (Fed.Cir.1991). In any event, the patent owner bears the burden of proving by a preponderance of the evidence the quantum of damages, an issue of fact for which we review the jury's decision for substantial evidence. *Id.* at 1164 n. 2, 17 USPQ2d at 1925 n. 2.

[8] A decision to sanction a litigant pursuant to Fed.R.Civ.P. 37 is one that is not unique to patent law, *DH Tech., Inc. v. Synergystex Int'l, Inc.*, 154 F.3d 1333, 1343, 47 USPQ2d 1865, 1873 (Fed.Cir. 1998), and we therefore apply regional circuit law to that issue, *Midwest Indus., Inc. v. Karavan Trailers, Inc.*, 175 F.3d 1356, 1359, 50 USPQ2d 1672, 1675 (Fed.Cir. 1999) (en banc in relevant part). Because the Eighth Circuit, the pertinent regional circuit in this case, reviews the imposition of sanctions under Rule 37 for an abuse of discretion, *Givens v. A.H. Robins Co.*, 751

F.2d 261, 263 (8th Cir.1984), we will do the same.

On appeal Transclean raises a number of issues concerning damages and trademark infringement. First, Transclean argues that the court erred in disallowing the jury's award of a reasonable royalty on Bridgewood's proceeds from the sale of its business. Second, Transclean argues that the court abused its discretion by not awarding it enhanced damages and attorney fees for patent infringement under 35 U.S.C. §§ 284 and 285. Third, Transclean argues that the court erred in not awarding it attorney fees for pursuing the false advertising claim. Finally, Transclean argues that the court erred in granting summary judgment of noninfringement of its trademarks.

Bridgewood cross-appeals the court's judgments of patent validity and infringement. In particular, Bridgewood argues that the court erred in granting summary judgment that the '080 patent is not invalid for anticipation under 35 U.S.C. § 102. As to infringement, Bridgewood argues that the court abused its discretion when it estopped Bridgewood from contesting infringement of claims 1–4 and 12 as a discovery sanction and when it denied Bridgewood's motion for summary judgment of noninfringement of claim 13. We address each issue in turn.

A. *Patent Validity*

[9] Bridgewood asserts in its cross-appeal that the court erred when it granted summary judgment that neither the Becnel patent nor the Japanese patent anticipates the claims of the '080 patent. Although this is a cross-appealed issue, as is that on patent infringement, we deal with them first because they logically precede damages issues, which are the principally appealed issues. Bridgewood contends that the court misconstrued the phrase "means for equalizing the fluid flow" appearing in claim 1 by requiring that the fluid flow rate, rather than just the volume of fluid, be equalized. Based on its erroneously narrow construction of the claimed function, the court, according to Bridgewood, included extraneous structure in that corresponding to the "means for equalizing" limitation. Bridgewood asserts that the proper corresponding structure is a fresh fluid tank connected to a fresh fluid tube with a valve, a used fluid tank connected to a used fluid tube, and a source of pressurized air. Bridgewood contends that either the Becnel or Japanese patent discloses all of the minimum corresponding structure, and that the dependent claims recite well-known features that are also disclosed by the Becnel or Japanese patents.

Transclean responds that the court properly interpreted the term "flow" to mean a rate, not a volume, as the specification discloses that equalization of flow rates is the objective of the invention. Transclean further contends that the invention disclosed in the Becnel patent does not necessarily equalize flow rates, and that the Japanese patent discloses an apparatus that equalizes fluid weights, not flow rates.

We agree with Transclean that the claim phrase "equalizing the fluid flow" refers to a rate, not just a volume. To construe that phrase, we look to the specification for guidance, *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582, 39 USPQ2d 1573, 1577 (Fed.Cir.1996), and the specification clearly refers to the equalization of flow rates. For example, the patent describes problems that can occur in the prior art when the input flow rate of added fluid does not match the output flow rate of used fluid:

> [I]n the event fluid is allowed to drain *faster than the rate of addition* of fluid, the pump or torque converter in a

transmission is likely to be starved and then will become excessively hot under which conditions a transmission will self-destruct if permitted to continue in operation. On the other hand, should excessive fluid be added to build up an internal pressure within the transmission, there is a strong likelihood that seals for shafts and/or valves, bearings, or the like or other internal components, within the transmission, may be irreparably damaged with a resulting failure of the transmission under subsequent operating conditions.

'080 patent at col. 2, ll. 56–68 (emphasis added). Furthermore, the "Summary of the Invention" states that the invention solves those problems:

> Briefly, my invention is comprised of a fluid receiver for used fluid, a source of supply of fresh fluid, and a means for coordinating the introduction of fresh fluid with the draining of used fluid. With this in mind, it then only remains necessary to separate the fluid flow in a line that is external from the transmission so that *the used fluid is drained into a suitable fluid container and the new fluid is introduced at the same rate that the used fluid exits.* This can be accomplished in a number of ways, some of which will be described in more detail below.

Id. at col. 3, ll. 8–17 (emphasis added). Other passages in the patent echo the same idea. *E.g., id.* at col. 5, ll. 51–53; col. 8, ll. 1–8. Because the specification is clear as to the meaning of the phrase "equalizing the fluid flow," and no other intrinsic evidence suggests a different meaning for the phrase, we affirm the district court's construction of that phrase to require equalization of flow rate.

[10, 11] As the parties agree, the phrase "means for equalizing fluid flow" is a means-plus-function limitation governed by 35 U.S.C. § 112, ¶ 6, and the recited function is "equalizing fluid flow." To anticipate a claim reciting a means-plus-function limitation, the anticipatory reference must disclose the recited function identically. *Cf. Wenger Mfg., Inc. v. Coating Mach. Sys., Inc.*, 239 F.3d 1225, 1238, 57 USPQ2d 1679, 1689 (Fed.Cir.2001) ("Literal infringement of a means-plus-function claim requires that the accused device have structure for performing the identical function recited in the claim."). In this case, neither the Becnel nor the Japanese patent contains such a disclosure.

The Becnel patent is described in the '080 patent as equalizing overall fluid volume, not flow rate. '080 patent at col. 1, l. 38—col. 2, l. 68. Bridgewood presented testimony from Becnel, the inventor, that his invention could be operated in such a manner as to equalize flow rates. However, as the district court found, that manner is not disclosed in the Becnel patent itself, nor is it inherent in the operation of Becnel's invention. *Summary Judgment Opinion* at 1081 ("Becnel was able to read the fluid gauges, and then manually adjust the flow of fresh fluid so as to equalize the fluid flows, but neither his declaration, nor [Bridgewood's patent expert's] opinion, offer any explanation as to how a person of ordinary skill would read the Becnel Patent specification, and recognize that this method of flow equalization is necessarily present in the embodiment disclosed in Fig. 5."). We conclude, as did the district court, that Bridgewood did not raise any genuine issue of material fact regarding anticipation of claim 1 by the Becnel patent. Accordingly, we affirm the court's conclusion that Transclean is entitled to summary judgment of non-anticipation as to the Becnel patent.

[12] The Japanese patent likewise discloses equalization of fluid amount, but not necessarily fluid flow rates. Broadly speaking, the Japanese patent describes

an "ATF [automatic transmission fluid] exchanger device," Jap. Pat. 2–72299, abstract (English translation), which, like the invention described in the '080 patent, comprises a supply of fresh fluid, a receptacle for used fluid, and hoses for connection to a transmission's fluid circulation system. *Id.* However, the Japanese apparatus also includes scales for measuring the weights of the fresh fluid supplied and used fluid removed, as well as a "detection means so that the difference between the amount of fluid drained and the amount of fluid supplied is maintained within an indicated range; and which automatically balances the amount of fluid drained and fluid supplied within an indicated range." Thus, the Japanese patent explicitly discloses that fluid weight is equalized, not necessarily fluid flow rate. Although it is possible that the detection means could under some circumstances (*e.g.*, if the response time for the feedback loop is sufficiently fast) effectively equalize the flow rates as well, it is also possible for that not to be the case. Because anticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation, *Cont'l Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268–69, 20 USPQ2d 1746, 1749 (Fed.Cir.1991) (emphasis added), the Japanese patent cannot inherently anticipate the claims of the '080 patent. We conclude, as did the district court, that Bridgewood did not raise any genuine issue of material fact regarding anticipation of claim 1 by the Japanese patent, and we therefore affirm the court's conclusion that Transclean is entitled to summary judgment of non-anticipation as to the Japanese patent. Thus, we affirm the court's conclusion that the claims of the '080 patent are not invalid under 35 U.S.C. § 102 as being anticipated by the Becnel or Japanese prior art patents.

B. *Patent Infringement*

[13] Bridgewood argues that the court abused its discretion when, as a discovery sanction, it precluded Bridgewood from asserting that it did not infringe claims 1–4 and 12, and when it denied Bridgewood's motion for summary judgment of noninfringement of claim 13. Regarding the first point, Bridgewood argues that the court impermissibly invoked an extreme discovery sanction without notice to Bridgewood, that Transclean was not prejudiced by Bridgewood's lack of response to Transclean's interrogatory, and that the court avoided its duty to construe the claim and relieved Transclean of its burden to prove infringement. Transclean responds that it was prejudiced by the lack of discovery and that the sanction was consistent with precedent.

We conclude that the district court acted within its discretion when it granted summary judgment of infringement as a discovery sanction. Because the imposition of a discovery sanction is not a matter substantially related to patent law, we apply the law of the regional circuit, in this case the Eighth Circuit. *See Midwest Indus.*, 175 F.3d at 1359, 50 USPQ2d at 1675. Although the entry of judgment is an extreme sanction in the Eighth Circuit (and elsewhere), *Givens*, 751 F.2d at 264, we are not convinced that the district court abused its discretion. Transclean legitimately sought to discover Bridgewood's grounds for its defense of noninfringement and was entitled to a reply to its interrogatory. When Bridgewood chose not to respond before the closing of discovery other than to voice its belief that the '080 patent was invalid and unenforceable, *Summary Judgment Opinion* at 1059–60, 1060–61, the court was within its discretion to impose a sanction. The court found clear prejudice to Transclean, as it was precluded from conducting discovery on the in-

fringement issues. *Id.* at 1063. To hold that the district court abused its discretion would be to disarm the court of its important power to police its proceedings to ensure transparency and predictability and to discourage mischievous conduct by litigants. It will be a rare case in which we take such an action. Moreover, even if a lesser sanction such as exclusion of evidence may have been more closely tailored to the misconduct, *see Givens*, 751 F.2d at 263 (characterizing evidence exclusion as the "normal sanction" for failure to comply with a discovery deadline), the practical result would have been the same. Transclean's motion for summary judgment of infringement presented evidence sufficient to show infringement, and, in light of Bridgewood's non-response, that evidence was uncontradicted. Accordingly, we affirm the district court's grant of summary judgment of infringement of claims 1–4 and 12 of the '080 patent.

[14] As for the second alleged abuse of discretion, denial of Bridgewood's motion for summary judgment of noninfringement of claim 13, Bridgewood argues that the court misconstrued the phrase "exhibiting resilient characteristics" to mean "returning to an original shape after being deformed" or "returning to its original position after being compressed." *Summary Judgment Opinion* at 1087. Bridgewood contends that initial deformation of shape is inherent in the meaning of the expression and cites technical dictionary definitions in support of that contention. Under the correct construction of that expression, according to Bridgewood, the free-floating piston in its device does not "exhibit[ ] resilient characteristics." Moreover, Bridgewood contends that prosecution history estoppel and the all-limitations rule bar Transclean from asserting infringement under the doctrine of equivalents for that claim limitation because claim 13, in which it appears, was added during prosecution, whereas the originally submitted claims did not contain that limitation, and because vitiation of the "exhibiting resilient characteristics" limitation would result. Transclean responds that claim 13 requires only that "said means exhibit[ ] resilient characteristics," not that the means itself be "resilient." Transclean also cites common dictionary definitions and expert testimony in support of its view that the term "resilient" does not require initial deformation. Moreover, Transclean contends that claim 13 itself was never narrowed during prosecution and that Bridgewood's prosecution history estoppel argument was not raised in the district court and has therefore been waived.

Because we affirm the judgment of infringement of claims 1–4 and 12, we need not review the court's ultimate conclusion regarding infringement of claim 13. Bridgewood has already been held to be an infringer, and infringement of another claim does not increase its liability. *See Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1220, 36 USPQ2d 1225, 1231 (Fed.Cir.1995). However, to put to rest any doubts regarding the proper construction of claim 13, because the patent has not been shown to be invalid and the issue has been fully ventilated by the parties, we will address that issue. We agree with Bridgewood that the court misconstrued the term "resilient." Dictionaries, both general and technical, define the adjective "resilient" or its noun form "resilience" as encompassing that which returns to its original shape following a deformation in shape. *See, e.g., McGraw–Hill Dictionary of Scientific and Technical Terms* 1693 (5th ed.1994) (defining the term "resilience" as the "[a]bility of a strained body, by virtue of high yield strength and low elastic modulus, to recover its size and form following deformation"); *American Heritage Dictionary* 1535 (3rd ed.1992) (defining the term "resilient" as "returning to an original shape or position, as after having been

compressed"). The dissent, as did the district court, focuses on the word "or" in the preceding definition to support its view that the term "resilient" encompasses the returning to a position alone, without any shape deformation. We do not think that the use of the word "or" in that definition can overcome the meaning attributed to the term "resilient" by the patent's disclosure of only a flexible diaphragm dividing a tank into two chambers. *See* '080 patent; fig. 3; col. 4, ll. 54–55 (depicting and describing "a flexible rubber-like diaphragm"). Furthermore, to the extent there is a difference between the common and technical meanings of the terms, the term "resilient" is used in the '080 patent in a technical context to describe a component of a mechanical apparatus, and a technical dictionary is therefore a better source to inform the meaning of the term to a skilled artisan in this case. Moreover, we do not share the dissent's view that the phrase "exhibiting resilient characteristics" describes a function in a means-plus-function limitation. On the contrary, the means-plus-function limitation further defined in claim 13 is the "means for equalizing the flow" previously set forth in claim 1. *Id.* at col. 8, ll. 20–23, ll. 55–61. According to the claim language, the only function performed by that "means" is "equalizing the flow." The phrase "exhibiting resilient characteristics" is not a second function performed by that "means"; rather, the phrase further defines characteristics of that "means." It is therefore, appropriate, indeed mandatory under 35 U.S.C. § 112, ¶ 6, to look to the corresponding structure in the specification to ascertain the meaning of the phrase. As already noted, that corresponding structure, "a flexible rubber-like diaphragm," '080 patent, col. 4, ll. 54–55, is "resilient" in the sense that it tends to return to its original shape, not just its original position. We therefore conclude that the phrase "exhibiting resilient characteristics" in the '080 patent requires initial shape deformation. Because the jury's finding of infringement of claim 13 was premised on a construction of that phrase at odds with ours, we vacate the judgment of infringement of claim 13.

C. *Patent Infringement Damages*

[15] The jury awarded three types of damages for patent infringement: (1) $934,618 as a reasonable royalty on Bridgewood's sales of infringing devices; (2) $1,874,500 as "additional damages . . . necessary to adequately compensate for Bridgewood's infringement"; and (3) $2,708,225 as a reasonable royalty based upon Bridgewood's proceeds from the sale of its business to Century. *Damages Opinion* at 3. The court reversed the third award, holding that Transclean was not entitled to such an award as a matter of law. *Id.* at 65. As to the first and second, the court granted Bridgewood's motion for a new trial or remittitur in the amount of $1,874,500, the highest amount, based on the evidence, that the jury could have properly awarded for patent infringement. *Id.* at 61, 66. Transclean apparently accepted the remittitur.

Transclean appeals from the court's decision concerning the third award only. Transclean cites *Minco, Inc. v. Combustion Eng'g, Inc.*, 95 F.3d 1109, 40 USPQ2d 1001 (Fed.Cir.1996) in support of its argument that, because Bridgewood's sole source of revenue was an infringing product and Bridgewood generated $6,500,000 in goodwill from the sale of its business to Century, Transclean is entitled to recover the value of that goodwill. Transclean asserts that to allow Bridgewood to retain that windfall would create an incentive for others to infringe a patent and then sell their businesses.

Bridgewood responds that this case is distinguishable from *Minco* because that case involved lost profits, not a reasonable

royalty, and a reasonable royalty must be based on sales of infringing articles. Bridgewood contends that payment for goodwill is not the sale of infringing goods, was attributable to many factors other than the technology of its fluid changing machines, and that Transclean did not prove a nexus between the patent infringement and the value of the goodwill.

We agree with Bridgewood that *Minco* does not control this case. As indicated, it was a lost profits case, not one based on a reasonable royalty. Although *Minco* acknowledged that "fashioning an adequate damages award depends on the unique economic circumstances of each case," 95 F.3d at 1118, 40 USPQ2d at 1007, we held that the patent owner in that case could not recover damages based on the infringer's sale of its business. *Id.* at 1121. More specifically, the patent owner sought lost profits calculated as the difference between the sales price of the infringer's business and its expert's valuation of the business without the infringing devices. *Id.* at 1120. The patent owner asserted that the purchaser would have purchased its business instead of the infringer's, had it not been for the infringement, *id.*, and the excess sales price thus constituted part of the patent owner's lost profits. The district court did not accept that assertion, and we affirmed that decision. *Id.* at 1121. Furthermore, we explained that any award based on the infringer's sale of its business would be duplicative of the reasonable royalty the infringer had already received based on the infringer's sales of infringing goods. *Id.* ("The district court's reasonable royalty award already compensates [the patent owner] for any goodwill [the infringer] garnered by infringement."). Transclean's citation of *Minco* as controlling this case is thus unsound; it is an example of the unhelpful advocacy that is at times made to this court, in which counsel cites general language from a prior case, rather than its holding. In fact, the holding of *Minco* supports Bridgewood's position, not Transclean's.

We must analyze Transclean's claim for a percentage of Bridgewood's business sale proceeds as it was asserted, as a claim for a reasonable royalty, not for lost profits. Reasonable royalty damages for patent infringement arise from the fact of infringement, and the portion of the sales price consisting of intangible goodwill is not the sale of infringing goods. It is partial compensation for the sale of a business. Whether or not proceeds from the sale of a business including tangible assets such as infringing inventory would be compensable as a remedy for patent infringement we are not in a position to say; that case is not before us. What is clear is that the portion of a sales price consisting of goodwill, *i.e.*, compensation in excess of tangible assets, is not sales of infringing goods that can form the base for determination of a reasonable royalty. No such precedent exists, nor are we prepared to distort the statute to set one.

In addition, as a matter of proof, Transclean has not established the amount, if any, of a reasonable royalty on Bridgewood's sale of its business it is entitled to recover. Transclean had the burden of proving the amount of reasonable royalty damages it is entitled to recover. *Id.* The most relevant inquiry in that respect would seem to be the amount of the business's value that is attributable to the patent infringement. Transclean offered expert testimony that the entire goodwill above and beyond the value of Bridgewood's tangible assets was attributable to patent infringement because Bridgewood was a single product company and that product infringed Transclean's patent. *Damages Opinion* at 29–30. However, the district court disagreed, concluding that the opinion testimony was conclusory and belied by Bridgewood's arguments

that Bridgewood's goodwill was attributable to other factors (*e.g.*, customer lists, brand identity, product quality, and pricing). *Id.* at 30–31. We perceive no error in the district court's analysis or conclusion. Moreover, to the extent that Transclean argues that the goodwill was ultimately attributable to Bridgewood's sales of infringing machines, any award of reasonable royalty damages based on goodwill transferred when the business was sold would be a double recovery, as Transclean has already been awarded damages that fully compensate it for Bridgewood's past sales. *See Minco*, 95 F.3d at 1121, 40 USPQ2d at 1010 ("The district court's reasonable royalty award already compensates [the patent owner] for any goodwill [the infringer] garnered by infringement."). To the extent that the extra recovery Transclean seeks would be duplicative, we see no merit to Transclean's argument that Bridgewood is retaining a windfall that would create an incentive for infringers to sell infringing businesses with impunity.

For the reasons stated above, we conclude that the court did not err when it ruled that, as a matter of law, Transclean was not entitled to a reasonable royalty on proceeds from Bridgewood's sale of its business.

D. *Enhanced Damages*

[16] The jury found that Bridgewood's infringement was willful. Transclean argued to the jury that it made Bridgewood aware of the '080 patent, but that Bridgewood did not obtain an opinion of counsel and did not abate its manufacture or sale of the infringing machines. Bridgewood argued that the fact that it obtained its own patent on an automatic transmission fluid changing machine demonstrated a good faith belief that it was not an infringer. Bridgewood argued that when it received advice from its patent attorney concerning the patentability of its invention over the '080 patent, it received an implicit opinion of noninfringement. Although the jury agreed with Transclean that Bridgewood had willfully infringed the '080 patent, the court, after applying the factors set forth in *Read Corp. v. Portec, Inc.*, 970 F.2d, 816, 826–27, 23 USPQ2d 1426, 1435–36 (Fed.Cir.1992) (listing nine factors), declined to enhance the patent infringement damages. *Damages Opinion* at 13–22.

Transclean contends that the court abused its discretion by not enhancing the damages in light of the jury's finding of willfulness. Transclean also asserts that the court erroneously assumed that the only way it could enhance the damages was by trebling them, misunderstanding that an enhancement of less than trebling was a permissible option. Bridgewood responds that a finding of willful infringement does not mandate enhancement of damages, that the court did not misunderstand the law on enhancement, and that the court properly considered the *Read* factors.

[17] We agree with Bridgewood that the court acted within its discretion in not enhancing the damages award. Enhancement of damages under 35 U.S.C. § 284 involves the fact-finder determining that the infringer engaged in culpable conduct and the court exercising its discretion to determine whether and to what extent to enhance the damages. *Jurgens v. CBK, Ltd.*, 80 F.3d 1566, 1570, 38 USPQ2d 1397, 1399 (Fed.Cir.1996). The jury's finding of willfulness satisfies the first step, *see id.*, and is also one of the factors the court assesses in performing the second step, *see Read*, 970 F.2d at 827, 23 USPQ2d at 1435. However, there are other factors relevant to the second step. *See id.* (listing as factors: (1) deliberate copying; (2) infringer's investigation and good-faith belief of invalidity or non-infringement; (3) litigation conduct; (4) infringer's size and finan-

cial condition; (5) closeness of the case; (6) duration of the misconduct; (7) remedial action by the infringer; (8) infringer's motivation for harm; and (9) concealment). A finding of willful infringement "*authorizes* but does not *mandate* an award or increased damages." *Modine Mfg. Co. v. Allen Group, Inc.*, 917 F.2d 538, 543, 16 USPQ2d 1622, 1625 (Fed.Cir.1990). In this case, the court considered the pertinent *Read* factors carefully, *Damages Opinion* at 13–22, and although we may or may not have reached a different conclusion if we had been in the district court's shoes, we wear our own shoes. We review the court's analysis for an abuse of discretion, and we are satisfied that such an abuse did not occur.

We also agree with Transclean that the court did not erroneously assume that its only options were to treble the patent infringement damages or not enhance the damages at all. The court's opinion states, "In exercising our discretion to enhance damages, however, we are limited 'to a trebling of the basic damage award.' " *Damages Opinion* at 10 (quoting *Signtech USA, Ltd. v. Vutek, Inc.*, 174 F.3d 1352, 1358–59, 50 USPQ2d 1372, 1376 (Fed.Cir. 1999)). We read that statement, as it was intended in *Signtech*, to simply recognize the upper range of the possible enhancement. *See Signtech*, 174 F.3d at 1358–59, 50 USPQ2d at 1376 ("[T]he district court enjoys discretion to choose whether to award enhanced damages to the claimant *and in what amount.* This discretion, however is limited to a trebling of the basic damage award.") (citations omitted) (emphasis added). Elsewhere in the same opinion, the court makes statements recognizing that a range of enhancement is possible. *See Damages Opinion* at 8 (" '[T]he court determines, exercising its sound discretion, whether, *and to what extent*, to increase the damages award . . .' ") (quoting *Jurgens*, 80 F.3d at 1570, 38 USPQ2d at 1399) (emphasis added); *Damages Opinion* at 21 (" 'The paramount determination in deciding to grant enhancement *and the amount thereof* is . . .' ") (quoting *Read*, 970 F.2d, at 826, 23 USPQ2d at 1435) (emphasis added). *See also Modine*, 917 F.2d at 543 n. 3, 16 USPQ2d at 1625 n. 3 ("[T]he fact that the court's opinion focuses upon treble damages does not necessarily mean that the judge failed to *consider* lesser multiples of damages.").

E. *Attorney Fees*

After the trial, Transclean filed a motion for attorney fees, and the court granted that motion in part, awarding Transclean its attorney fees arising from arguing two issues. First, pursuant to 35 U.S.C. § 285, the court awarded Transclean attorney fees for defense of a charge of inequitable conduct asserted by Bridgewood. *Damages Opinion* at 27. The court's opinion does not address attorney fees under 35 U.S.C. § 285 except in relation to the inequitable conduct issue. Second, pursuant to Minnesota's private attorney general statute, Minn.Stat. § 8.31, the court awarded Transclean attorney fees for its successful claim that Bridgewood engaged in false advertising by promoting its transmission fluid changing machine as replacing "100%" or "every drop" of transmission fluid. *Id.* However, the court later revoked that award for two reasons: Transclean had unclean hands by promoting its own service as a "total" fluid exchange, and Transclean did not object to Century's use of the same advertisements after Century had purchased Bridgewood and taken a license to the '080 patent from Transclean.

Transclean now argues that the court abused its discretion by not awarding Transclean attorney fees under 35 U.S.C. § 285 for its entire patent infringement claim when the jury determined that Bridgewood's infringement was willful and

by not stating its reasons for declining to award attorney fees apart from those related to inequitable conduct. Transclean further argues that the court abused its discretion by not ultimately awarding attorney fees under Minn.Stat. § 8.31 for its false advertising claim. Bridgewood responds that a finding of willful infringement does not mandate a determination that a case is exceptional, as that term is used in 35 U.S.C. § 285, and that not every exceptional case is deserving of an award of attorney fees. Bridgewood further responds that the court set forth legitimate reasons for not awarding attorney fees for the false advertising claim and thus acted within its discretion.

[18, 19] With regard to attorney fees for patent infringement, we agree with Bridgewood. Transclean is correct in stating the general rule that the district court must normally explain why it decides that a case is not exceptional under 35 U.S.C. § 285 when a factual finding of willful infringement has been established and, if exceptional, why it decides not to award attorney fees, *S.C. Johnson & Son, Inc. v. Carter-Wallace, Inc.*, 781 F.2d 198, 201, 228 USPQ 367, 369 (Fed.Cir.1986). However, we have recognized an exception to that general rule in cases where the record adequately sets forth grounds for affirming the district court's actions. *Carroll Touch, Inc. v. Electro Mech. Sys. Inc.*, 15 F.3d 1573, 1584, 27 USPQ2d 1836, 1845 (Fed.Cir.1993) (citing *Consol. Al. Corp. v. Foseco Int'l, Ltd.*, 910 F.2d 804, 814, 15 USPQ2d 1481, 1488–89 (Fed.Cir.1990)). In this case, the court's careful analysis of the *Read* factors regarding enhancement of damages suffices as grounds for affirming the court's implicit conclusion that the infringement case was not exceptional within the meaning of 35 U.S.C. § 285.

[20, 21] With regard to attorney fees for false advertising, we agree with Bridgewood. Transclean's claim for attorney fees arising from the false advertising cause of action was based on Minn.Stat. § 8.31. The purpose of that statute is to encourage private parties to police unlawful trade practices affecting the public interest. *Ly v. Nystrom*, 615 N.W.2d 302, 313–14 (Minn.2000). The court determined that, while Transclean's cause of action against Bridgewood for false advertising was on its face one that qualified for attorney fees under the statute, *Attorney Fees Opinion* at 11, Transclean's own use of advertising that was arguably equivalent in falsity and Transclean's tolerance of Century's use of the same advertising when it licensed Transclean's patent erased any public benefit accruing from the successful action against Bridgewood, *id.* at 12–14. The district court's reasoning is sound, and we discern no abuse of discretion in its decision not to award Transclean attorney fees for its false advertising claim.

F. *Trademark Infringement*

[22] Transclean brought a cause of action for trademark infringement, asserting that Bridgewood infringed Transclean's TOTAL FLUID EXCHANGE and TOTAL FLUID X-CHANGE unregistered trademarks under section 43(a) of the Lanham Act, 15 U.S.C. § 1125(a)(1), and Minnesota law. The court granted Bridgewood's motion for summary judgment of noninfringement on the ground that there was no genuine issue of material fact relating to Transclean's adequate usage of the marks in commerce. *Summary Judgment Opinion* at 1094–95. Transclean argues that a genuine issue of material fact regarding that issue was raised by an affidavit from James P. Viken, Transclean's CEO and inventor on the '080 patent, stating that Transclean had used the marks on its products and documents since 1994. *Id.* at 1093–94. Bridgewood responds that the affidavit is conclusory and

does not designate specific facts concerning the marks' usage.

[23] We agree with Bridgewood that Transclean failed to raise a genuine issue of material fact as to nondescriptive usage of the mark on the goods. We apply Eighth Circuit law to this issue, and the Eighth Circuit has recognized the universal requirement for actual usage of the mark in commerce, *First Bank v. First Bank Sys., Inc.*, 84 F.3d 1040, 1044 (8th Cir.1996). Use of the mark on documents does not satisfy the usage requirement when the mark can be affixed to the goods themselves, *Elec. Communications, Inc. v. Elec. Components for Industry Co.*, 443 F.2d 487, 492 (8th Cir.1971), as is the case here, *Summary Judgment Opinion* at 1094. Furthermore, the usage of the marks must be as a source identifier rather than as a description of the goods' qualities. *First Bank*, 84 F.3d at 1044. In this case, the Viken affidavit is deficient in two ways, even if assumed to be accurate. First, the reference to documents is irrelevant, *Elec. Communications*, 443 F.2d at 492–93. Second, on its face, the affidavit does not purport to show that the use was as a source identifier. Indeed, the record evidence shows that the marks were used in a purely descriptive manner, *e.g.*, "TFX TOTAL FLUID EXCHANGE SYSTEM FOR AUTOMATIC TRANSMISSIONS by Transclean Corp." Accordingly, the court did not err when it concluded that the Viken affidavit failed to raise a genuine issue of material fact regarding usage of the Transclean's marks, and we affirm the court's grant of summary judgment in favor of Bridgewood on the trademark claims.

CONCLUSION

We commend the district court for its thorough and competent handling of a complex case involving a large number of difficult issues. We affirm all aspects of the court's decision except one. The court did not err in granting summary judgment that the '080 patent is not anticipated by either the Becnel or Japanese prior art patents. Nor did the court err in granting summary judgment that Bridgewood did not infringe Transclean's trademarks, or in granting Bridgewood's post-trial motion for reversal of the jury's award of damages based on a reasonable royalty of Bridgewood's sale of its business. Furthermore, the court did not abuse its discretion in entering a judgment of infringement of claims 1–4 and 12 as a discovery sanction against Bridgewood. Nor did the court abuse its discretion when it declined to award Transclean enhanced damages and attorney fees under the patent statute or Minnesota law. However, the court did err when it construed the phrase "exhibiting resilient characteristics" in claim 13 of the '080 patent, and we therefore vacate the jury's determination, based on the court's erroneous claim construction, that Bridgewood infringed claim 13. Accordingly, we

AFFIRM–IN–PART and *VACATE–IN–PART.*

CLEVENGER, Circuit Judge, dissenting in part.

I agree with the majority's resolution of the validity, damages, and attorney fees issues as well as its determination that the district court did not abuse its discretion in precluding Bridgewood from asserting noninfringement of claims 1–4 and 12 as a sanction for various discovery abuses. Furthermore, I agree with the majority that the district court properly granted summary judgment to Bridgewood on Transclean's trademark infringement claim. However, in my view the majority's construction of the term "resilient" in claim 13 is unduly narrow and departs from the term's ordinary meaning. There-

fore, I respectfully dissent from that portion of the majority's opinion vacating the district court's claim construction and the jury's finding of infringement as to that claim.

This case asks us to decide the meaning of the word "resilient." That word is not defined in the specification. Indeed, "resilient" appears in the patent exactly once in claim 13:

> The apparatus of claim 1 in which the means for equalizing the flow is comprised of means disposed intermediate the fluid receiver and source, said means *exhibiting resilient characteristics* for exerting a force, related to the pressure existing in the fluid circulation circuit of said transmission and said receiver, upon the fluid in said source.

U.S. Patent No. 5,318,080, col. 8, lines 55–61 (emphasis added). Because the patentee has not chosen to be his own lexicographer in this instance, "resilient" should carry its ordinary meaning in the art. Transclean asserts that "resilient" encompasses the ability to return to an original shape *or* position after being compressed, while Bridgewood argues that a resilient means must be capable of returning to an original shape *and* position after being compressed-in other words, that it must be inherently elastic.

To help us divine the meaning of "resilient," Transclean has provided dictionary definitions of "resilient" as well as expert testimony regarding what one of skill in the art would understand the term to mean. In contrast, Bridgewood proffers definitions of "resilience" from technical dictionaries. The district court properly rejected Bridgwood's definitions of "resilience" and adopted instead the ordinary meaning of the actual claim term, resili*ent*. The majority, based on the supposed superiority of technical dictionaries over ordinary dictionaries, prefers Bridgewood's definition.

The district court gave the word "resilient" its ordinary dictionary meaning, possessing "the capability of 'returning to an original shape *or position*, as after having been compressed.' " *Transclean Corp. v. Bridgewood Services, Inc.*, 77 F.Supp.2d 1045, 1087 (D.Minn.1999) (quoting *American Heritage Dictionary* 1535 (3d ed.1992) (emphasis added)). In other words, the broad term "resilient characteristics" can include a variety of different properties such as the ability to return to an original position after being exposed to a force, or the ability to return to an original shape after having been deformed. This meaning is in accord with the definition found in other common dictionaries. *See, e.g., Websters Third New International Dictionary (unabridged)* 1932 (defining resilient as "returning freely to a previous position, shape *or* condition: as a: moving swiftly back . . . b: capable of withstanding shock without permanent deformation or rupture . . . c: SPRINGY . . . ." (first emphasis added)); *Oxford English Dictionary* 714 (2d Ed.1989) (defining resilient as "1. Returning to the original position; springing back, recoiling, etc." and "2. Resuming the original shape or position after being bent, compressed, or stretched"); *Random House Webster's Unabridged Dictionary* 1638 (2d ed.1993) (defining resilient as "1. springing back; rebounding" and "2. returning to the original form *or* position after being bent, compressed, or stretched") (emphasis added). This meaning is in accord with the expert testimony proffered by Transclean, which explained that the patent uses the term resilient to mean "returning to the, some earlier position . . . or shape."

To support its proposed definition, Bridgewood cites various technical dictionaries that, supposedly, define " 'resilient' or 'resilience.' " A closer examination of these sources reveals, however, that the technical definitions provided by Bridge-

wood in fact relate the definition of "resilience" and not "resilient." And, unlike "resilient," "resilience" generally refers to the stored energy of a strained-and typically elastic-material. For example, *Van Nostrand's Scientific Encyclopedia* 2673 (8th ed.1995) defines resilience as follows: "resilience of a body measures the extent to which energy may be stored in it by elastic deformation." The *Dictionary of Mechanical Engineering* 314 (4th ed.1996) defines resilience as "[t]he stored energy of a strained or elastic material, such as in a compressed spring or in rubber dampers, which have inherent damping properties." *See also Chambers Dictionary of Science and Technology* 980 (1999) (defining resilience as the "[s]tored energy of a strained material, or the work done per unit volume of an elastic material by a bending moment, force, torque or shear force, in producing strain").

The majority chooses to rely upon Bridgewood's proffered definitions of "resilience" rather than the ordinary meaning of the actual claim term, "resilient," for two reasons. First, the majority finds that technical dictionaries are generally superior to common dictionaries. While dicta in *Bell Atlantic Network Services, Inc. v. Covad Communications Group, Inc.*, 262 F.3d 1258, 1267, 59 USPQ2d 1865, 1870 (Fed.Cir.2001), states the view that technical dictionaries are preferred to common dictionaries, neither that case nor the case upon which it relied, *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 45 USPQ2d 1429 (Fed.Cir.1998), involved a conflict between a common dictionary definition and that found in a scientific treatise-and neither does this case. The technical definitions are simply inapt because they define the wrong word-resilience instead of resilient. Indeed, the "common dictionaries" rejected by the majority are the only sources before the court that define *both* resilient and resilience, and notably, they define resilience in the same way as the supposedly superior technical dictionaries. For example, *Webster's Third New International Dictionary* 1932 (1993) defines resilience as follows:

> 1a: an act of springing back: REBOUND, RECOIL, ELASTICITY b: capability of a strained body to recover its size and shape after deformation, esp. when the strain is caused by compressive stresses-called also *elastic resilience* *2: the recoverable potential energy of an elastic solid body or structure due to its having been subjected to stress not exceeding the elastic limit.*

(Second emphasis added.) While it may often be preferable to look to a technical dictionary or treatise to provide the technical definition of a term as understood by practitioners of a particular art, I think that preference must fade when the technical dictionary does not provide a definition of the precise term used in the claim language. Therefore, I would hold that the trial court properly adopted the common dictionary definition of "resilient" as proffered by Transclean.

The majority shores up its view of the correct meaning for "resilient" by holding that the phrase "exhibiting resilient characteristics for exerting a force" does not describe part of the function of the "means for equalizing the flow" limitation. I disagree with that holding, for it is clear to me that the "exhibiting resilient characteristics" phrase does define function. If I am correct on this point, then of course it is impermissible to define the function by reference to structure disclosed in the written description. Function must be defined by reference to ordinary principles of claim interpretation, before proceeding to determine corresponding structure. *See Kemco Sales, Inc. v. Control Papers Co.*, 208 F.3d 1352, 1361, 54 USPQ2d 1308, 1313 (Fed.Cir.2000). The majority does not disagree with me on this point: if the phrase in question defines function, then

resort to the specification to find structure to define the function is simply wrong, and ordinary tools of claim interpretation apply.

Instead, the majority holds that the phrase in question is actually part of the means for equalizing the flow, and that resort to the specification is required to find the structure corresponding to the means limitation. Thus, from the specification the majority fetches the flexible rubber-like diaphragm, and thereupon concludes that "exhibiting resilient characteristics" must require initial shape deformation because that is the characteristic of the diaphragm.

The majority's rationale is self-destructive. If the diaphragm is indeed the structure that corresponds to the "means for equalizing the flow" limitation-as both parties and all the judges on the case agree-then the majority must come to grips with the stark fact that the jury found that the piston structure in Bridgewood's device is structurally equivalent, for § 112 ¶ 6 infringement purposes, to the diaphragm disclosed in Figure 3. Indeed, the case was submitted to the jury precisely to resolve disputed issues of fact on the structural equivalence of the accused piston and the diaphragm structure. No question has been raised that substantial evidence does not support the jury's verdict. Consequently, if, as the majority holds, "exhibiting resilient characteristics for exerting a force" must be understood as merely "further defin[ing] the structure of [the] means," *ante* at 1375, there is no possible basis for disturbing the jury's verdict of infringement.

In short, the majority is wrong on any interpretation of the disputed phrase. If the phrase describes function, it must be interpreted by ordinary interpretative canons, as did the district court. If the phrase is to be interpreted as part of the means limitation, as the majority holds, then the jury verdict of infringement must stand. Either way, the jury verdict of infringement cannot properly be upset, and I respectfully dissent from the majority on this point.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex Parte Foster
Appeal No. _____

Applicant:	Michael B. Foster
Serial Number:	09/838,968
Filed:	April 20, 2001
Confirmation No.:	1662
Art Unit:	1653
Examiner:	Kam, Chih Min
Title:	**METHOD OF OPTIMIZING GROWTH HORMONE REPLACEMENT**
Attorney Ref. No.:	RENAS-03

Cincinnati, Ohio 45202 November 18, 2003

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

BRIEF ON APPEAL

This is an appeal from the decision of the Examiner in a final Office Action dated May 19, 2003 (paper no. 13). For purpose of appeal, the claims 1-3, 5-11, and 13-16 should read as indicated in Appendix A to this brief.

R al Party in Interest

The subject application is owned by Renasci, Inc., d/b/a/ Renasci Anti-Aging Center, Scottsdale, Arizona.

Related Appeals and Interferences

None.

Status of the Claims

Original claims 1-18, filed with this application, were rejected in a first Office Action (paper no. 3) dated March 8, 2002, as follows: claims 1 - 18 under 35 U.S.C. §112, ¶ 2; and claims 1, 4-10, 12-14, and 18 under 35 U.S.C. § 102(b) over Chien.

In an Amendment filed April 26, 2002, applicant amended original claims 11, 12 and 17 and added a new method claim 19.

Claims 1-19 were rejected in a final Office Action (paper no. 6) dated July 16, 2002 as follows: claims 1-19 under 35 U.S.C. § 112, ¶ 2; claims 1, 4-10, 12-14, 18, and 19 under 35 U.S.C. § 102(b) over Chien.

In a response dated September 16, 2002 applicant canceled claims 12, 17, and 19, and amended independent claims 1 and 10 as suggested by the Examiner during an interview with applicant's undersigned representative on April 25, 2002, and amended dependent claims 2, 11, and 15.

In an Office Action Summary (paper no. 10) dated December 2, 2002, the Examiner withdrew rejection of claims 1-18 under 35 U.S.C. § 112 ¶ 2 and claims 1, 4-10, 12-14, 18, and 19 under 35 U.S.C. § 102(b) over Chien; the Examiner rejected claims 2, 3, 7, 10, 11, 13, 15, and 16 under 35 U.S.C. § 112 ¶ 2; and rejected claims 1, 4, 7-10, and 13 under 35 U.S.C. § 102(b) over Drake; and rejected claims 1, 4-10, 13, 14, and 18 under 35 U.S.C. § 102(b) over Murray.

In a response dated February 10, 2003 applicant canceled claims 4, 18, and amended dependent claims 7 and 13 and filed an Inventor's Declaration.

In a final Office Action Summary (paper no. 13) dated May 19, 2003, the Examiner withdrew the rejections of claims 7 and 13 under 35 U.S.C. § 112, ¶ 2; withdrew the rejection of claim 4 under 35 U.S.C. §102(b) over Drake; and withdrew the rejection of claims 4 and 18 under 35 U.S.C. §102(b) over Murray. The Examiner maintained rejection of claims 2, 3, 10, 11, 13, 15, and 16 under 35 U.S.C. §112, ¶ 2; rejected claims 1, 7-10 and 13 under 35 U.S.C. §102(b) over Drake; and rejected claims 1, 5-10, 13 and 14 under 35 U.S.C. §102(b) over Murray.

Applicant filed a Notice of Appeal on September 19, 2003 for claims 1-3, 5-11, and 13-16.

Status of Amendments

In a final Office Action dated May 19, 2003, the Examiner rejected claims 2, 3, 10, 11, 13, 15 and 16 as indefinite and claims 1, 5-10, 13 and 14 as anticipated. Applicant filed a Notice of Appeal on September 19, 2003 for claims 1-3, 5-11, and an

Appeal Brief is being timely filed on November 18, 2003. Applicant also timely filed on November 6, 2003, a Supplemental After Final Amendment to correct a typographical error for claim 10 to include a phrase missing in the clean copy but, as the Examiner indicated, was recited in the marked copy of the Amendment filed September 23, 2003.

Summary of the Invention

The inventive method replenishes human growth hormone (hGH) in an adult by first determining the optimal dose for that individual, and then administering that optimal dose as a maintenance dose to replenish hGH. Human growth hormone is the only active administered; there are no other hormones or other actives in the composition (page 3, lines 19-21).

The maintenance dose is determined by administering an initial hGH dose, then determining the individual's response to the initial dose. The individual's initial response may be determined by assaying the level of insulin growth factor-1 (IGF-1), which is produced in response to hGH and mediates the anabolic effects of hGH in adults (page 6, lines 8-15). The initial dose is then serially increased, until a maintenance hGH dose optimized to the individual (page 6, lines 16-25) is determined.

The maintenance dose is then administered. It may be administered on a daily basis. Alternatively, it may be administered on a monthly basis, by calculating the daily dose and taking into account an individual's bioavailability data. The composition may be administered in a time-released formulation, such as a microsphere. This flexibility provides convenience to the individual in terms of dosing.

Issues

Whether claim 2, 3, 10, 11, 13, 15 and 16 are indefinite under 35 U.S.C. § 112, ¶ 2, and whether claims 1, 5-10, 13, and 14 are unpatentable under 35 U.S.C. 102 (b) as anticipated by Drake and Murray.

Grouping of Claims

The rejected claims do not stand together. Each of the two claims sets are rejected on a different statutory basis (claims 2, 3, 10, 11, 13, 15, and 16 as indefinite; claims 1, 5-10, 13, and 14 as anticipated). Whether the claims are found to be indefinite does not affect the proper application of prior art for purposes of anticipation, and whether the claims are found to be anticipated does not affect their definiteness.

Therefore, independent claims 1, 10 and 20, and the claims depending thereon involve different determinations of what is definite, and what is anticipated by the cited art. Accordingly the patentability of these claims involve separate determinations that are independent of each other.

Argument

Claims 2, 3, 10, 11, 13, 15 and 16 are definite under 35 U.S.C. § 112, ¶ 2.

Independent claim 10, and dependent claims 11 and 13, are not indefinite because the missing phrase is included in the claims (see Status of Amendments).

Applicant has filed a Supplemental After Final Amendment on November 6, 2003, as suggested by Examiner during the telephone interview with applicant's undersigned representative on November 3, 2003, to correct a typographical error for claim 10 to include the missing phrase thus conforming the clean and marked-up copies. Applicant notes that the Examiner indicated in the Office Action of May 19, 2003 that the missing phrase was not in the clean copy but was recited in the marked copy of the Amendment filed September 23, 2003.

The standard for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Miles Labs, Inc. v. Shandon,* Inc., 997 F.2d 870 (Fed. Cir. 1993) (Appendix B)). With respect to claims 2, 3, 15, and 16, one skilled in the art would understand the bounds of calculating a daily dose to a monthly dose using individualized bioavailability data.

As stated in the specification, further pointed out in applicant's Declaration (submitted with the Amendment dated February 10, 2003), an individual's response to serially increased doses of hGH are evaluated, usually over one to two months. The dose is adjusted at about two to four week intervals, in a range equal to that of the initial dose. The specification also provides examples of these calculations. It teaches that a male receives an initial dose of 2 µg/kg/day for two to four weeks, then receives a dose of 6 µg/kg/day for two to four weeks, then receives a dose of 8 µg/kg/day for two to four weeks, etc., until the maintenance dose is achieved. It also teaches that a female receives an initial dose of 4 µg/kg/day, then receives a serially increased dose of 8 µg/kg/day for two to four weeks, then receives a dose of 12 µg/kg/day for two to four weeks, etc., until the maintenance dose is achieved.

The maintenance dose is converted from a daily to a monthly dose, based on individualized bioavailability data. One skilled in the art, who had calculated the daily maintenance dose, would know how to convert this information to a monthly dose using bioavailability data. For example, a standard pharmacology text (Goodman and Gilman's The Pharmacological Basis of Therapeutics (Pergamon Press, New York 1990; pp. 5-6, 10-13, 20-32) (Appendix C)) states that bioavailability data indicate the extent to which a drug reaches its site of action, or a biological fluid from which the drug has access to its site of action (page 5). "Individualized bioavailability", as applicant claims, simply encompasses the individual pharmacodyanic and pharmacokinetic parameters of an individual: namely, hepatic and renal clearance (pages 21-23), volume of distribution which relates the amount of drug in the body to concentration of the drug in blood or plasma (pages 23-25), the half-life of a drug in the body (pages 25-26), and the extent and rate of availability which involve the drug's bioavailability and rate of absorption (pages 26-28). These are parameters that one of ordinary skill in this art would use to determine the bounds of these claims.

Thus, applicant's specification as to maintenance or monthly dose, and individualized bioavailability data for making these determinations is definite because one ordinarily skilled in the art would know how to interpret the meaning of these terms.

With respect to Drake and Murray, these are cited as anticipating the invention (35 U.S.C. § 102(b) and § 102(a), respectively). To anticipate, a reference must disclose each and every limitation of the claims. *Transclean Corp. v. Bridgewood Serv.*, 290 F.3d 1364 (Fed. Cir. 2002) (Appendix D)). Neither Drake or Murray disclose

applicant's administration of an individualized dose, and thus do not anticipate applicant's claimed method.

As explained in the Foster Declaration, there is considerable variation in setting the target IGF-1 level to determine the optimal range of hGH. To prevent the harmful results that can ensue, as also explained in the Declaration, the inventive method determines an individualized optimal dose. Neither Drake nor Murray disclose applicant's method for individualizing the optimal hGH replenishing dose selecting a dose producing an optimal replenishment.

Drake does not disclose determining an optimal dose from individualized dosing. Instead, Drake uses a target level of IGF-1 from which he determines his optimal dose. This is not "individualized", in contrast, it is uniform because it has a single target: the IGF-1 level in the upper part of the age-related reference range.

The fact that Drake's dose accounts for age does not make his method of dosing "individualized", because Drake's method would dose to target the same IGF-1 level in all individuals of the same age. However, applicant's method would calculate their individual response to initial and increased doses regardless of whether individuals are the same age, and administer the optimal dose for that individual.

Drake also does not disclose determining a response to a serially increased dose that is predicated on the initial dose that was administered. In Drake's method, there is always the same increase, so that there is no variation in the magnitude.

In contrast, applicant claims an individualized dose where a response to an initial dose is determined, then a response to a serially increase dose is determined,

then the dose that produces optimal replenishment is selected from the serially increased dose and administered as a maintenance dose. This is not disclosed by Drake.

Murray does not anticipate the claimed method. In fact, Murray itself states that "the ideal dosing regimen and determinants of the maintenance dose have, however, yet to be elucidated" (page 537, Summary section). Thus, Murray does not disclose applicant's claimed "optimal response" or "optimal replenishment". The Examiner's rejection, however, contradicts the reference in finding that Murray has, in the Examiner's view, determined the ideal dosing regimen and determinants of the maintenance dose, simply by correlating it with IGF-1 levels. The examiner's view is incorrect on two accounts: (1) it applies Murray in direct contradiction to its express disclosure, and (2) it ignores the individualized dosing requirement of applicant's method to determine an individual's optimal response.

As explained in the Foster Declaration with supporting clinical analysis, the claimed method, which produces an optimal clinical response while avoiding side effects, does in fact reach the "ideal regimen" sought by Murray.

Unless each and every element of a claim is described in a reference, it is error to reject a claim based on that reference. Therefore, applicant's claims are patentable under 35 U.S.C. § 102(b) and § 102(a).

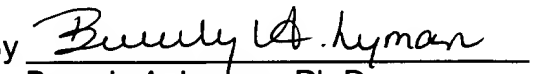
Summary

For the foregoing reasons, appellant believes that the Examiner's rejections of claims 1-3, 5-11, and 13-16 were erroneous, and reversal of the decision is respectfully requested.

Enclosed is a check in the amount of $165.00 for the filing of this Brief. Should any further fees be indicated herein, authorization is given to charge or credit any overpayment to Deposit Account No. 23-3000.

Respectfully submitted,

WOOD, HERRON & EVANS, L.L.P.

By 
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APPENDIX A

1. A method of replenishing human growth hormone (hGH) in an adult human comprising administering a composition consisting essentially of recombinant hGH in an individualized dose to replenish hGH, said individualized dose determined by

(1) determining a response of said human to an initial dose of said composition administered on a daily basis,

(2) thereafter determining a response of said human to serially increased doses of said composition administered on a daily basis,

(3) selecting said dose of composition from (2) producing an optimal replenishment to administer as a maintenance dose, and

(4) thereafter administering said dose from (3) to replenish hGH.

2. The method of claim 1 wherein said maintenance dose is calculated from a daily dose to a monthly dose based on individualized bioavailability data and is administered monthly.

3. The method of claim 2 wherein said dose comprises a microsphere formulation of said agent.

4. CANCELED.

5. The method of claim 1 wherein said human is a male and said maintenance dose is in the range of about 10-14 μg/kg/day.

6. The method of claim 1 wherein said human is a female and said maintenance dose is in the range of about 14-20 μg/kg/day.

7. The method of claim 1 wherein said response comprises increased insulin like growth factor-1 levels.

8. The method of claim 1 wherein said human is a male and said initial dose is about 2 μg/kg/day.

9. The method of claim 1 wherein said human is a female and said initial dose is about 4 μg/kg/day.

10. A method of providing an adult human with human growth hormone (hGH) comprising

administering a composition consisting essentially of recombinant hGH to said human on a daily basis at an initial dose to produce an initial response to said composition,

thereafter administering at least one serially increased initial dose of said composition on a daily basis and evaluating said human's response to said serially increased dose to produce an individualized optimal response to said composition, and

thereafter administering said dose producing said optimal response as a maintenance dose.

11. The method of claim 10 wherein said dose producing said optimal response is calculated from a daily dose to a monthly dose based on individualized bioavailability data and is administered monthly.

12. CANCELED.

13. The method of claim 10 wherein said response is evaluated by evaluating a level of insulin like growth factor-1.

14. A method of optimizing human growth hormone (hGH) replacement in an adult human comprising

(1) administering an initial dose of hGH in the range of about 2 µg/kg/day hGH to about 4 µg/kg/day on a daily basis for about three to four weeks and determining insulin like growth factor 1 (IGF-1) levels,

(2) thereafter administering serially increasing doses of said initial hGH dose on a daily basis for about three to four weeks and determining IGF-1 levels,

(3) selecting said hGH dose from (2) producing optimal hGH replenishment to administer as a maintenance dose, and

(4) thereafter administering said maintenance dose in the range of about 10 µg/kg/day hGH to about 20 µg/kg/day hGH to said individual.

15. The method of claim 14 wherein said maintenance dose is calculated from a daily dose to a monthly dose based on individualized bioavailability data and is administered monthly.

16. The method of claim 15 wherein said maintenance dose comprises hGH formulated in microspheres.

17-19. CANCELED.

APPENDIX B

Miles Labs, Inc. v. Shandon, Inc.,
997 F.2d 870 (Fed. Cir. 1993)

The undisputed evidence is that David Walbert, the same attorney who did most of the work for the State in this case at the rate of $100 per hour, submitted an affidavit in a 1986 proceeding, two years before this one began, that his rate to private clients was $140 per hour, which he swore was below average for attorneys of his skill and expertise. In that same affidavit, Walbert characterized Laughlin McDonald, Brooks' lead counsel in the present case, as "the best known and most respected voting rights attorney in the United States." There was no evidence offered in this case that Walbert's skill, expertise, and career had peaked in 1986 and had been on a sharp downward slide since that time, nor was there any evidence that Walbert had lowered his opinion of his own professional worth or his opinion of McDonald. Under these circumstances, it was clear error for the district court panel to rely so heavily on the rate paid to opposing counsel. We remand the case to it so that the hourly rate can be fixed free of this error.

[10] In reconsidering on remand the hourly rate or rates at which to compensate Brooks' counsel, the court should bear in mind our prior direction that a district court "must explain its reasoning in determining a reasonable attorney's fee to give this court an adequate and informed basis for review." *Gilmere v. City of Atlanta*, 931 F.2d 811, 814 (11th Cir.1991). We have held that the court did not err in setting the range of prevailing rates in this case at $125–$175. In determining the actual rate or rates of compensation within that range for Wilde and McDonald, the court should consider the skill, experience, and reputation of each of the two lawyers, the nature and difficulty of the work performed, and other relevant factors. The court should also consider the hourly rates these two attorneys had been paid in similar litigation at or before the time of this lawsuit. As mentioned previously, Wilde was awarded fees in three other voting rights cases at the rate of $125 per hour. McDonald had been awarded $175 per hour in 1990, but that was the highest amount he had ever been awarded.

We do not mean that the district court panel must necessarily re-open the record on remand; the evidence on these issues appears adequately developed. Nor do we mean to diminish the district court's autho ty to utilize its discretion and its own exp tise in considering these matters and awa ing reasonable attorney's fees. *See Norm* 836 F.2d at 1303 (noting that courts may u own knowledge and experience in determ ing reasonable fees). Indeed, we remand t matter rather than decide it ourselves p cisely because it is the district court pa that has the discretion to exercise, not

III. CONCLUSION

We REMAND this case to the distr court panel for the limited purpose of c recting two aspects of its calculation of att ney's fees. First, the court is to exclu from the number of hours for which comp sation is awarded any hours spent on before December 1, 1989 in opposition preclearance by the Department of Justic Second, the court is to reset, within the $1 to $175 range, the hourly rate for each Brooks' counsel, without regard to the r paid to counsel for the State of Georg After making those two corrections, the co should recalculate the attorney's fees awa and enter an appropriate order.

MILES LABORATORIES, INC. and Triangle Biomedical Equipment, Inc., Plaintiffs/Cross–Appellants,

v.

SHANDON INC. and Shandon Southe Products Limited, Defendants–Appellants.

Nos. 92–1358, 92–1387.

United States Court of Appeals, Federal Circuit.

June 14, 1993.

Rehearing Denied; Suggestion for Rehearing In Banc Declined Sept. 1, 1993.

Action was brought for infringement patent for light microscopy apparatus

8. The same goes for costs associated with such work. See n. 3, above.

tissue processing and patent for processing method. The United States District Court, Western District of Pennsylvania, Gustave Diamond, Chief Judge, held claims of method patent invalid for obviousness, sustained validity of apparatus patent, and found infringement of both patents. On cross appeals, the Court of Appeals, Rader, Circuit Judge, held that: (1) apparatus patent was not invalid for indefiniteness or for failure to meet enablement or utility requirements; (2) accused devices infringed apparatus patent under doctrine of equivalents; (3) claim of method patent addressing means of reusing solutions by returning unused quantities to storage container with pressure was invalid for obviousness; and (4) District Court properly invalidated dependent claims in light of stipulation that claim invalid for obviousness was representative.

Affirmed.

1. Federal Courts ⇐754

Court of Appeals accepts legal conclusions of district court unless incorrect as matter of law. Fed.Rules Civ.Proc.Rule 52(a), 28 U.S.C.A.

2. Federal Courts ⇐776

Court of Appeals does not review de novo proceedings of district court. Fed. Rules Civ.Proc.Rule 52(a), 28 U.S.C.A.

3. Federal Courts ⇐754, 850

To win reversal, party must show that district court committed reversible legal error or relied upon factual findings which were clearly erroneous in light of trial record. Fed.Rules Civ.Proc.Rule 52(a), 28 U.S.C.A.

4. Federal Courts ⇐851, 852

"Clearly erroneous" standard does not entitle Court of Appeals to reverse district court's findings simply because it would have decided case differently; where fact finder's account of evidence is plausible in light of entire record or where it chooses one of two permissible views of evidence, it has committed no clear error. Fed.Rules Civ.Proc.Rule 52(a), 28 U.S.C.A.

See publication Words and Phrases for other judicial constructions and definitions.

5. Patents ⇐314(5)

Compliance with statute requiring patent to be sufficiently definite is question of law. 35 U.S.C.A. § 112.

6. Patents ⇐101(6)

"Distinctly claiming" requirement of statute requiring patents to be sufficiently definite means that claims must have clear and definite meaning when construed in light of complete patent document. 35 U.S.C.A. § 112.

7. Patents ⇐101(6)

Test for definiteness is whether one skilled in art would understand bounds of patent claim when read in light of specification; it is sufficient for purposes of statute that claims read in light of specification reasonably apprise those skilled in art of invention's scope. 35 U.S.C.A. § 112.

8. Patents ⇐101(6)

Degree of precision necessary for adequate patent claims under statute ensuring definiteness of claim language is function of nature of subject matter. 35 U.S.C.A. § 112.

9. Patents ⇐101(6)

Question of whether invention described by claims is operable is irrelevant to issue of whether patent is sufficiently definite. 35 U.S.C.A. § 112.

10. Patents ⇐49

Even if claims of patent for light microscopy tissue processing apparatus did cover only unvented containers, patent was not invalid for lack of utility, as record showed that even unvented containers would be operative; there was testimony that, without vents, collapsible solution containers could permit transfer of fluids by pressure changes. 35 U.S.C.A. § 101.

11. Patents ⇐101(6)

Preferred embodiment described in patent specification for light microscopy tissue processing apparatus disclosed "vented" solution containers and, thus, claims read in light of specification reasonably apprised those skilled in art of claimed invention, as re-

quired to satisfy requirement of definiteness. 35 U.S.C.A. § 112.

12. Patents ⇐101(6)

Patent for light microscopy apparatus for tissue processing disclosed adequate information to enable skilled artisan to make and use claimed invention, particularly as preferred embodiment described in specification disclosed "vented" solution containers. 35 U.S.C.A. § 112.

13. Patents ⇐101(1)

Claim interpretation is first step in two-part infringement determination.

14. Patents ⇐314(5)

Claim interpretation proceeds as question of law.

15. Patents ⇐324.5

When trial resolves factual disputes underlying meaning of claim terms, Court of Appeals reviews those findings under clearly erroneous standard.

16. Patents ⇐167(1), 168(2.1)

In interpreting disputed patent claim terms, trial court considers specification and prosecution history.

17. Patents ⇐226.6

After interpreting patent claim, final step of infringement analysis determines whether accused device is within scope of claim.

18. Patents ⇐226.6, 237

To infringe, accused device must embody exactly each patent claim limitation or its equivalent.

19. Patents ⇐167(1)

Term "cabinet," within meaning of patent claim for light microscopy apparatus for tissue processing, meant single enclosure for various parts of apparatus; embodiment illustrated in patent specification disclosed single cabinet comprised of number of sections, including numerous reagent bottles, processing chamber, paraffin containers and control module.

See publication Words and Phrases for other judicial constructions and definitions.

20. Patents ⇐235(2)

Accused devices in action alleging infringement of patent for light microscopy apparatus for tissue processing did not literally infringe single cabinet limitation of patent, as devices consisted of three modules as opposed to one; term "cabinet," within meaning of claim limitation, meant single enclosure for various parts of apparatus.

21. Patents ⇐237

Accused devices infringed patent for light microscopy apparatus for tissue processing under doctrine of equivalents, even though devices consisted of three modules, as opposed to single cabinet for various components of apparatus; patent did not specify that cabinet contained all components of invention, and devices achieved substantially same result as patent, as they were systems for processing tissue under completely automatic sequence in closed system without requiring substantial movement of specimens.

22. Patents ⇐237

Infringement under doctrine of equivalents requires showing that accused device performs substantially same function, in substantially same way, to achieve substantially same result as claimed device.

23. Patents ⇐237

Doctrine of equivalents prevents pirating of patentee's invention in absence of literal infringement when liability is nevertheless warranted and, thus, doctrine prevents risk of injustice that may result from limited focus on words alone.

24. Patents ⇐237

Limitations on functions of invention in claims, not elements or functions of accused device, establish reference point for doctrine of equivalents.

25. Patents ⇐237

Infringement under doctrine of equivalents does not vanish merely because device performs functions in addition to those performed by claimed device.

26. Patents ⇐16(1), 314(1)

Ultimate legal conclusion of obviousness is question of law, but rests on several factual

inquiries: scope and content of prior art; differences between prior art and claims; level of ordinary skill in art at time of invention; and objective evidence of nonobviousness. 35 U.S.C.A. § 103.

27. Patents ⇐324.5

Court of Appeals reviews factual underpinnings for legal conclusion of obviousness under clearly erroneous standard. 35 U.S.C.A. § 103.

28. Patents ⇐16.17

Claim of patent for light microscopy tissue processing method addressing means of reusing solutions by returning unused quantities to storage container with pressure was invalid for obviousness; prior art of histological equipment taught flow of liquids in tissue processing apparatuses from one location to another with vacuum-pressure, and patent covering electron microscopy tissue processor disclosed processor which discharged used fluids into waste tank, rather than storage container, after processing. 35 U.S.C.A. § 103.

29. Patents ⇐36(1)

Objective indicia of nonobviousness, if present, would have weighed in favor of nonobviousness of patent claim, though lack of such evidence did not weigh in favor of obviousness. 35 U.S.C.A. § 103.

30. Patents ⇐32

Party challenging validity of patent claim, absent pretrial agreement or stipulation, must submit evidence supporting conclusion of invalidity for each contested claim. 35 U.S.C.A. § 282.

31. Patents ⇐314(6)

Where parties stipulate to "representative" claims, validity resolution for representative claims applies to other claims of patent as well. 35 U.S.C.A. § 282.

32. Stipulations ⇐14(1)

In light of stipulation making claim of patent representative for other claims, district court properly invalidated dependent claims upon determining that representative claim was invalid for obviousness. 35 U.S.C.A. § 282.

Arnold Sprung, Sprung Horn Kramer & Woods, Tarrytown, NY, argued for plaintiffs/cross-appellants. With him on the brief was Nathaniel D. Kramer.

Robert D. Yeager, Kirkpatrick & Lockhart, Pittsburgh, PA, argued for defendants-appellants. With him on the brief were Christine R. Ethridge and Melvin C. Snyder, III.

Before PLAGER, Circuit Judge, SMITH, Senior Circuit Judge, and RADER, Circuit Judge.

RADER, Circuit Judge.

Miles Laboratories, Inc. and Triangle Biomedical Equipment, Inc., sued Shandon Inc. and Shandon Southern Products Limited, for infringement of U.S. Patent Reissue No. 29,073, entitled "Light Microscopy Processing Apparatus" ('073),* and U.S. Patent No. 4,001,460, entitled "Light Microscopy Processing Method" ('460). The United States District Court for the Western District of Pennsylvania held claims 1, 2, and 4–7 of the '460 patent invalid for obviousness, sustained the validity of the '073 patent, and found infringement of both patents. *Miles Lab., Inc. v. Shandon, Inc.*, No. 86–2404, 1992 WL 503432 (W.D.Pa. Mar. 11, 1992) (*Miles I*); *Miles Lab., Inc. v. Shandon, Inc.*, No. 86–2404 (W.D.Pa. Apr. 14, 1992) (*Miles II*). Because the record adequately supports the district court's decision, this court affirms.

BACKGROUND

Tissue processing is the treatment of tissue specimens to facilitate viewing them under a microscope. The process exposes the tissue specimens to a series of chemical solutions (reagents) in sequence. The '460 patent claims a method and the '073 patent an apparatus for tissue processing. Except for the claims, the two patents have identical specifications.

* U.S. Patent Reissue No. 29,073 issued on December 14, 1976 as a reissue of U.S. Patent No. 3,892,197, which issued on July 1, 1975.

Under the method accomplished by the apparatus, a central processing chamber confines the tissue specimens under a sealed cover where they remain fixed during treatment with various fluids and paraffin. Once embedded in paraffin, the specimens can be sliced into very thin sections for microscopic viewing. The treatment takes place when a vacuum draws the fluids and paraffin into the central chamber. After proper exposure, pressure in the central chamber expels the fluids back to their storage containers. Thus, the entire processing occurs without tampering with the tissue specimens.

In 1986, Miles sued Shandon for infringement of both patents. The district court held a bench trial in 1988. The district court determined that the doctrine of laches did not bar this action and that claim 1 of the '460 patent was invalid under 35 U.S.C. § 103. *Miles I*, slip. op. at 30. The district court also upheld the validity of the '073 patent and found infringement of both patents. *Id.*

Later, the district court clarified its earlier decision and added the '460 patent's dependent claims 2 and 4–7 to its obviousness ruling. *Miles II*, slip op. at 1. In addition, the district court enjoined Shandon from further infringement of the '073 patent. *Id.* Shandon appeals the validity determination on the '073 patent and the infringement rulings. Miles cross-appeals the invalidity determination on the '460 patent.

DISCUSSION

Standard of Review

[1] This court reviews the district court's fact finding under the "clearly erroneous" standard of Rule 52(a):

> Findings of fact, whether based on oral or documentary evidence, shall not be set aside unless clearly erroneous, and due regard shall be given to the opportunity of the trial court to judge of the credibility of the witnesses.

Fed.R.Civ.P. 52(a) (1988); *see Heisig v. United States*, 719 F.2d 1153, 1158 (Fed.Cir. 1983). This court accepts the legal conclusions of the district court unless incorrect as a matter of law. *Id.*

[2–4] This court does not review *de novo* proceedings of the district court. *Medtronic, Inc. v. Daig Corp.*, 789 F.2d 903, 904, 229 USPQ 664, 666 (Fed.Cir.), *cert. denied*, 479 U.S. 931, 107 S.Ct. 402, 93 L.Ed.2d 355 (1986). To win reversal, a party must show that the district court committed reversible legal error or relied upon factual findings which were clearly erroneous in light of the trial record. *Id.* 789 F.2d at 904–05. In addition, the "clearly erroneous" standard does not entitle this court to reverse the district court's finding simply because it would have decided the case differently. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1375, 231 USPQ 81, 87 (Fed.Cir.1986), *cert. denied*, 480 U.S. 947, 107 S.Ct. 1606, 94 L.Ed.2d 792 (1987). Where the factfinder's account of the evidence is plausible in light of the entire record or where it chooses one of two permissible views of the evidence, it has committed no clear error. *Id.*

The '073 Patent

On the last day of trial, Shandon moved to introduce an infringement defense that the '073 patent was invalid for indefiniteness under 35 U.S.C. § 112, ¶ 2 (1988). The district court, however, upheld the validity of the '073 patent. On appeal, Shandon alleges the claims of the '073 patent omit the requirement for "vented" solution containers and therefore do not distinctly claim the disclosed invention.

Validity

[5, 6] Shandon challenged the claims of the '073 patent as indefinite under § 112, ¶ 2. Compliance with § 112, ¶ 2 is a question of law. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed.Cir.1986). Section 112, paragraph 2, states:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

35 U.S.C. § 112, ¶ 2. The "distinctly claiming" requirement means that the claims must have a clear and definite meaning when con-

strued in the light of the complete patent document. *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 452, 227 USPQ 293, 296 (Fed.Cir.1985). Section 112 thus ensures definiteness of claim language. *See In re Zletz*, 893 F.2d 319, 322, 13 USPQ2d 1320, 1322 (Fed.Cir.1989).

[7, 8] The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Orthokinetics*, 806 F.2d at 1576. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more. *Hybritech*, 802 F.2d at 1385. The degree of precision necessary for adequate claims is a function of the nature of the subject matter. *Id.*

[9] At trial, a Miles expert, Mr. Kocsis, stated:

> Q Now, reading these claims [of the '073 patent], which we have just discussed, did you see any mention in any of these claims of vented containers or reagent bottles, or anything like that?
>
> A No, I did not.
>
> . . . .
>
> Q Now, that single machine, as described in the '460 and '073 patents, requires that a vent to atmosphere be present in each solution container in order for the machine to transfer solutions from a solution container to a processing chamber and back, is that correct?
>
> A That's correct.

Relying on these isolated statements, Shandon contends that the claims do not specify vented solution containers. Without vented containers, Shandon contends, the claims do not describe a workable invention. Without vents, Shandon asserts, the invention cannot change pressure to draw fluids into and out of the central treatment chamber.

Shandon's argument is irrelevant to definiteness under § 112, ¶ 2. The invention's operability may say nothing about a skilled artisan's understanding of the bounds of the claim. Shandon's argument is possibly relevant, however, to the enablement requirement of § 112, ¶ 1, or to utility under § 101.

[10] Construed as a challenge to utility or enablement, Shandon's argument nevertheless fails. Mr. Kocsis testified that the claimed tissue processors would operate with or without vents in the solution containers. Without vents, collapsible solution containers could permit the transfer of fluids by pressure changes. The district court correctly concluded that "the record shows that even unvented containers would be operative." *Miles II*, slip op. at 4. Thus Shandon did not show a lack of utility, even if the claims cover only unvented containers.

[11, 12] The trial court also determined that the claims, read in light of the specification, covered both unvented containers and vented containers. In fact, the preferred embodiment described in the specification discloses "vented" solution containers:

> Referring again to FIG 3, the previously referred to solution containers 15 (with operating numbers 1 through 10) have respective caps 55 for refilling the containers. Suitable air vents 56, indicated by dashed lines, are provided in each cap 55, but are preferably kept extremely small so as to limit any admission of moisture.

Col. 6, lines 3–9. Therefore, the claims read in light of the specification reasonably apprise those skilled in the art of the claimed invention. Moreover, the record shows that the patent disclosed adequate information to enable a skilled artisan to make and use the claimed invention. *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941, 15 USPQ2d 1321, 1329 (Fed.Cir.), *cert. denied*, 498 U.S. 920, 111 S.Ct. 296, 112 L.Ed.2d 250 (1990).

Appellant incorrectly characterized its validity challenge as a claim definiteness issue—a characterization which the district court followed, at least in name. Nonetheless, the district court made proper findings and correctly concluded that appellant did not rebut the presumed validity of the claims.

Infringement

The district court determined that the accused devices, known as the HYPERCENTER and the HYPERCENTER 2, infringed the '073 patent literally, or in the alternative, under the doctrine of equivalents. *Miles I*,

slip op. at 28–30. On appeal, Shandon argues that the district court misconstrued the "cabinet" limitation of the claims.

[13–18] This court reviews a trial court's infringement findings under the "clearly erroneous" standard. *Charles Greiner & Co. v. Mari-Med Mfg., Inc.*, 962 F.2d 1031, 1034, 22 USPQ2d 1526, 1528 (Fed.Cir.1992); *Insta-Foam Prods., Inc. v. Universal Foam Sys., Inc.*, 906 F.2d 698, 702, 15 USPQ2d 1295, 1297 (Fed.Cir.1990). Claim interpretation is the first step in the two-part infringement determination. *Greiner*, 962 F.2d at 1034. Claim interpretation proceeds as a question of law. *Id.* When a trial court, however, resolves factual disputes underlying the meaning of claim terms, this court reviews these findings under the clearly erroneous standard. *Id.* In interpreting disputed claim terms, the trial court considers the specification and the prosecution history. *Id.* After interpreting the claim, the final step of the infringement analysis determines whether the accused device is within the scope of the claim. *Id.* To infringe, an accused device must embody exactly each claim limitation or its equivalent. *Id.*

The district court determined that the HYPERCENTERs contained every limitation set forth in claim 1 of the '073 patent. *Miles I*, slip op. at 28. In reaching this conclusion, the district court construed the cabinet limitation of claim 1 to define an enclosure for the various elements of the processing apparatus. *Id.* The court also determined that the HYPERCENTERs consisted of three modules: a module which housed the operating controls, a module which housed the reagent storage bottles, and a module which contained the central processing chamber and the paraffin baths. The district court concluded that the separate modules of the HYPERCENTER collectively formed a cabinet. *Id.*

[19] The district court properly construed the term "cabinet" to mean a single enclosure for the various parts of the apparatus. The claims, specification, and drawings disclose a single cabinet enclosing the tissue processing apparatus. The embodiment illustrated in the patent specification disclosed a single cabinet comprised of a number of sections, including numerous reagent bottles, a processing chamber, paraffin containers, and a control module. Moreover, Webster's defines "cabinet" as "1 a case or cupboard with drawers or shelves for holding or storing things . . . 2 a boxlike enclosure." *Webster's New World Dictionary*, 193 (3d col. ed. 1988).

[20] The HYPERCENTERs, however, consist of three modules as opposed to one. "Module" is defined as "any of a set of units, as cabinets, designed to be arranged or joined in a variety of ways." *Webster's* at 872. Because three does not equal one, the district court clearly erred in finding that the HYPERCENTERs (consisting of three cabinets) literally infringed the single cabinet limitation of the '073 patent.

[21, 22] This court, however, concludes that the district court did not err in determining that the HYPERCENTERs infringed the '073 patent under the doctrine of equivalents. Infringement under the doctrine of equivalents requires a showing that the accused device performs substantially the same function, in substantially the same way, to achieve substantially the same result as the claimed device. *Malta v. Schulmerich Carillons, Inc.*, 952 F.2d 1320, 1325, 21 USPQ2d 1161, 1165 (Fed.Cir.1991), *cert. denied*, —— U.S. ——, 112 S.Ct. 2942, 119 L.Ed.2d 566 (1992) (citing *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608, 70 S.Ct. 854, 856, 94 L.Ed. 1097 (1950)).

[23] The doctrine of equivalents prevents the pirating of the patentee's invention in the absence of literal infringement when liability is nevertheless warranted. *Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1564, 15 USPQ2d 1039, 1044 (Fed. Cir.1990). The doctrine of equivalents thus prevents the risk of injustice that may result from a limited focus on words alone. *Laitram Corp. v. Cambridge Wire Cloth Co.*, 863 F.2d 855, 856–57, 9 USPQ2d 1289, 1291 (Fed. Cir.1988), *cert. denied*, 490 U.S. 1068, 109 S.Ct. 2069, 104 L.Ed.2d 634 (1989).

Shandon argues that the district court did not determine that the HYPERCENTERs achieved "substantially the same result" as

the '073 patent. Shandon contends that the intended result of the '073 patent is unification of the various components. Shandon alleges that HYPERCENTERs achieve safety and operational advantages by separating the components.

The '073 patent achieves an enclosed tissue processing system. The district court stated:

> The '073 patent discloses an *apparatus* for fixing and processing the tissue specimens. It is an improvement over the prior art because it represents the first completely automatic system for allowing light microscopy tissue to be processed under a completely automatic sequence in an entirely closed system and without requiring substantial movement of the specimens.

Miles I, slip op. at 3–4 (citation omitted). This result does not change merely because Shandon separated certain components of the system into discrete modules.

In addition, the '073 patent does not specify that the cabinet contains all components of the invention. Rather claim 1 specifies an "air pump means ... mounted proximate said cabinet." The '073 patent, col. 11, lines 17–19. Claim 1 also claims "electrical control means ... mounted proximate said chamber." *Id.* col. 12, lines 1–3. Therefore, although claim 1 may have a cabinet limitation, not all components of the tissue processor must be within the cabinet. Indeed, the specification states that "the controls could be mounted in a separate cabinet." *Id.* col. 10, lines 34–35.

[24, 25] The limitations and functions of the invention in the claims, not the elements or functions of the accused device, establish the reference point for the doctrine of equivalents. *Insta-Foam*, 906 F.2d at 702. Infringement under the doctrine does not vanish merely because the accused device performs functions in addition to those performed by the claimed device. *Id.* Regardless of separation into modules, Shandon's system is still a "completely automatic system for allowing light microscopy tissue to be processed under a completely automatic sequence in an entirely closed system and without requiring substantial movement of the specimens." *See Miles I*, slip op. at 3–4. Thus, the HYPERCENTERs achieved substantially the same result as the '073 patent.

To allow Shandon to escape infringement simply because it used separate cabinets, as opposed to a single cabinet, is the exact type of injustice the doctrine of equivalents prevents. *See Laitram Corp.*, 863 F.2d at 856–57. This court discerns no clear error in the district court's finding of infringement under the doctrine of equivalents.

The '460 Patent

The district court held claim 1 of the '460 patent invalid for obviousness under 35 U.S.C. § 103 (1988). *Miles I*, slip op. at 16–17. The district court later held the dependent claims of the '460 patent (claims 2, 4–7) invalid by virtue of claim 1's invalidity. *Miles II*, slip op. at 2.

35 U.S.C. § 103—Obviousness

[26, 27] The ultimate legal conclusion of obviousness is a question of law. *Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 989, 6 USPQ2d 1601, 1606 (Fed.Cir.1988). The analysis of obviousness, however, rests on several factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims; (3) the level of ordinary skill in the art at the time of invention; and (4) objective evidence of nonobviousness. *Id.* (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18, 86 S.Ct. 684, 693–694, 15 L.Ed.2d 545 (1966)). This court reviews these factual underpinnings for the legal conclusion of obviousness under the "clearly erroneous" standard. *Specialty Composites*, 845 F.2d at 989. The facts stated herein are based on district court findings not found to be clearly erroneous or otherwise not in dispute.

[28] The prior art in this instance included U.S. Patent No. 3,526,203 (the '203 patent), U.S. Patent No. 3,227,130 (the Weiskopf patent), and the Lipshaw Manufacturing Corporation's "Fluid X Changer." The '203 patent covers an electron microscopy tissue processor. Electron microscopy differs from light microscopy in that the former requires only very small tissue specimens. With

small tissue specimens, electron microscopy does not need to reuse processing reagents. Nonetheless, the specification of the '203 patent provides: "it will be apparent that the processor of the invention may be used for processing the larger sized tissue particles which are intended for light microscopy examination." *Miles I*, slip op. at 10 (quoting U.S. Patent No. 3,526,203, col. 8, lines 5–8). The claims of the '203 patent disclose the vacuum component of the '460 patent. Furthermore, the '203 patent suggests a solution to the problem resolved by claim 1 of the '460 patent, namely, a means of reusing a solution by returning unused quantities to the storage container with pressure.

The specification of the '203 patent provides:

> In this regard it should be noted that the practice in electron microscopy work is not to reuse the solutions and in the system of the invention only fresh solution is transferred through the lines and valves connecting the containers with the processing chamber. If the particular solutions are required to be pumped back to the containers after use appropriate pumping and switching controls would have to be provided.

U.S. Patent No. 3,526,203, col. 8, lines 12–19. Although electron microscopy does not reuse solutions, the '203 patent suggests to a skilled artisan the reuse of solutions by pumping them back to their storage containers.

The "Fluid X Changer" (a device used for staining slides bearing tissue specimens) also suggests transfer of solutions by pressure. Moreover, the Weiskopf patent discloses a tissue processor which transfers solutions by pressure controls. Thus, the prior art of histological equipment taught the flow of liquids in tissue processing apparatuses from one location to another with vacuum-pressure.

The differences between the prior art and claim 1 of the '406 patent were minor and achievable by simple modification. Moreover, the prior art references collectively suggest the engineering necessary to achieve these modifications. Simply put, the '203 patent discloses a tissue processor which does not reuse fluids but instead discharges them into a waste tank after processing. By running a line from the processing chamber back to the fluid storage containers (rather than to the waste tank), the '203 patent would anticipate the '460 patent.

[29] The level of ordinary skill in the art suggests as well a thorough knowledge of the principles of fluid transfer using pressure-vacuum pumps, valves, and conduits at the time of the '460 patent's development. Finally, Miles did not show objective indicia of non-obviousness. Such evidence, if present, would weigh in favor of non-obviousness, although the lack of such evidence does not weigh in favor of obviousness. *See, e.g., Custom Accessories, Inc. v. Jeffrey–Allan Indus., Inc.*, 807 F.2d 955, 1 USPQ2d 1196, 1199 (Fed.Cir.1986). Miles presented no evidence, for instance, that its device represented a substantial share of any definable market. Miles also did not offer evidence on factors such as long-felt need or teaching away in the prior art.

In sum, the district court concluded:

> On the basis of the *Graham* test, therefore, we conclude that claim 1 of the '460 patent is invalid under 35 U.S.C. § 103 because the subject matter of claim 1 as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains.

Miles I, slip op. at 16–17. This court finds no error (and certainly no clear error) with the district court's obviousness findings and conclusion. Therefore this court affirms the district court's determination of invalidity of claim 1 of the '460 patent.

[30, 31] In its later opinion, the district court clarified its earlier decision and also held dependent claims (2 and 4–7) of the '460 patent invalid. *Miles II*, slip op. at 1–2. Section 282 requires an independent analysis of the validity of each claim. 35 U.S.C. § 282 (1988); *Ortho Pharmaceutical Corp. v. Smith*, 959 F.2d 936, 942, 22 USPQ2d 1119, 1124 (Fed.Cir.1992). A party challenging the validity of a claim, absent a pretrial agreement or stipulation, must submit evidence

supporting a conclusion of invalidity for each contested claim. *Id.* Where the parties stipulate to "representative" claims, however, a validity resolution for the representative claims applies to the other claims as well. *See Panduit Corp. v. Dennison Mfg. Co.*, 836 F.2d 1329, 1330–31, 5 USPQ2d 1266, 1267–68 (Fed.Cir.1987).

[32] In an April 1988 pretrial "Stipulation of Agreed Fact, Law of the Case and Questions of Law," the parties agreed:

> The '460 patent contains seven claims. Claim 1 is the only independent claim. Claims 2 through 7 depend directly or indirectly from claim 1. Consequently, claim 1 is the broadest claim and can be considered to be representative of the claims in this patent.

Miles II, slip op. at 2 n. 1. This stipulation of the parties made claim 1 a representative for the other claims in the patent. Thus, the parties, their counsel, and the trial court understood that the result the court reached for claim 1 would bind all other claims. Therefore, this court affirms the district court's invalidation of the dependent claims of the '460 patent.

The district court also determined that the accused device infringed the '460 patent. Because it affirms the district court's invalidity findings, this court need not reach the district court's infringement determination. *See Dana Corp. v. IPC Ltd. Partnership*, 860 F.2d 415, 417, 8 USPQ2d 1692, 1694 (Fed. Cir.1988), *cert. denied*, 490 U.S. 1067, 109 S.Ct. 2068, 104 L.Ed.2d 633 (1989).

CONCLUSION

For the above stated reasons, this court affirms the district court's finding of infringement of the '073 patent and the upholding of its validity. This court also affirms the district court's holding that claims 1, 2, and 4–7 of the '460 patent are invalid due to obviousness.

COSTS

Each party shall bear its own costs for this appeal.

AFFIRMED.

APPENDIX C

Goodman and Gilman's
The Pharmacological Basis of Therapeutics
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GOODMAN and GILMAN's

The Pharmacological Basis of Therapeutics

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In this textbook, reference to proprietary names of drugs is ordinarily made only in chapter sections dealing with preparations. Such names are given in SMALL-CAP TYPE, usually immediately following the official or nonproprietary titles. Proprietary names of drugs also appear in the Index.

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to a steady state. For a weak base with a pK_a of 4.4 ($BH^+ \rightleftharpoons B + H^+$), the ratio would be reversed, as would the thick horizontal arrows in Figure 1–2, which indicate the predominant species at each pH. These considerations have obvious implications for the absorption and excretion of drugs, as will be discussed more specifically below. The establishment of concentration gradients of weak electrolytes across membranes with a pH gradient is a purely physical process and does not require an active transport system. All that is necessary is a membrane preferentially permeable to one form of the weak electrolyte and a pH gradient across the membrane. The establishment of the pH gradient is, however, an active process.

Bulk flow through intercellular pores is the major mechanism of passage of drugs across most capillary endothelial membranes, with the important exception of the central nervous system (CNS) (*see* below). These intercellular gaps are sufficiently large that diffusion across most capillaries is limited by blood flow and not by the lipid solubility of drugs or pH gradients. This is an important factor in filtration across glomerular membranes in the kidney (*see* below). Tight junctions are characteristic of capillaries of the CNS and a variety of epithelia. Intercellular diffusion is consequently limited. Pinocytosis, the formation and movement of vesicles across cell membranes, has been implicated in drug absorption. However, the quantitative significance of pinocytosis is questionable.

Carrier-Mediated Membrane Transport. While passive diffusion through the bilayer is dominant in the absorption and distribution of most drugs, more active and selective mechanisms can play important roles. Active transport of some drugs occurs across neuronal membranes, the choroid plexus, renal tubular cells, and hepatocytes. The characteristics of active transport—selectivity, competitive inhibition by congeners, a requirement for energy, saturability, and movement against an electrochemical gradient—may be important in the mechanism of action of drugs that are subject to active transport or that interfere with the active transport of natural metabolites or neurotransmitters. The term *facilitated diffusion* describes a carrier-mediated transport process to which there is no input of energy, and movement of the substance in question thus cannot occur against an electrochemical gradient. Such mechanisms, which may also be highly selective for specific conformational structures of drugs, are necessary for the transport of endogenous compounds whose rate of movement across biological membranes by simple diffusion would otherwise be too slow.

DRUG ABSORPTION, BIOAVAILABILITY, AND ROUTES OF ADMINISTRATION

Absorption describes the rate at which a drug leaves its site of administration and the extent to which this occurs. However, the clinician is primarily concerned with a parameter designated as *bioavailability*, rather than absorption. Bioavailability is a term used to indicate the extent to which a drug reaches its site of action *or* a biological fluid from which the drug has access to its site of action. For example, a drug that is absorbed from the stomach and intestine must first pass through the liver before it reaches the systemic circulation. If the drug is metabolized in the liver or excreted in the bile, some of the active drug will be inactivated or diverted before it can reach the general circulation and be distributed to its sites of action. If the metabolic or excretory capacity of the liver for the agent in question is great, bioavailability will be substantially decreased (the so-called first-pass effect). This decrease in availability is a function of the anatomical site from which absorption takes place; other anatomical, physiological, and pathological factors can influence bioavailability (*see* below), and the choice of the route of drug administration must be based on an understanding of these conditions. Moreover, factors that modify the absorption of a drug can change its bioavailability.

Factors That Modify Absorption. Many variables, in addition to the physicochemical factors that affect transport across membranes, influence the absorption of drugs. Absorption, regardless of the site, is dependent upon drug solubility. Drugs given in aqueous solution are more rapidly absorbed than those given in oily solution, suspension, or solid form because they mix more readily with the aqueous phase at the absorptive site. For those given in solid form, the rate of dissolution may be the lim-

iting factor in their absorption. Local conditions at the site of absorption alter solubility, particularly in the gastrointestinal tract. Aspirin, which is relatively insoluble in acidic gastric contents, is a common example of such a drug. The concentration of a drug influences its rate of absorption. Drugs ingested or injected in solutions of high concentration are absorbed more rapidly than are drugs in solutions of low concentration. The circulation to the site of absorption also affects drug absorption. Increased blood flow, brought about by massage or local application of heat, enhances the rate of drug absorption; decreased blood flow, produced by vasoconstrictor agents, shock, or other disease factors, can slow absorption. The area of the absorbing surface to which a drug is exposed is one of the more important determinants of the rate of drug absorption. Drugs are absorbed very rapidly from large surface areas such as the pulmonary alveolar epithelium, the intestinal mucosa, or, in a few cases after extensive application, the skin. The absorbing surface is determined largely by the route of administration. Each of these factors separately or in conjunction with one another may have profound effects on the efficacy and toxicity of a drug.

Enteral (Oral) vs. Parenteral Administration. Often there is a choice of the route by which a therapeutic agent may be given, and a knowledge of the advantages and disadvantages of the different routes of administration is then of primary importance. Some characteristics of the major routes employed for systemic drug effect are compared in Table 1–1.

Oral ingestion is the most common method of drug administration. It is also the safest, most convenient, and most economical. Disadvantages to the oral route include the incapability to absorb some drugs because of their physical characteristics (*e.g.*, polarity), emesis as a result of irritation to the gastrointestinal mucosa, destruction of some drugs by digestive enzymes or low gastric pH, irregularities in absorption or propulsion in the presence of food or other drugs, and necessity for cooperation on the part of the patient. In addition, drugs in the gastrointestinal tract may be metabolized by the enzymes of the mu-

Table 1–1. SOME CHARACTERISTICS OF COMMON ROUTES OF DRUG ADMINISTRATION *

ROUTE	ABSORPTION PATTERN	SPECIAL UTILITY	LIMITATIONS AND PRECAUTIONS
Intravenous	Absorption circumvented Potentially immediate effects	Valuable for emergency use Permits titration of dosage Suitable for large volumes and for irritating substances, when diluted	Increased risk of adverse effects Must inject solutions *slowly*, as a rule Not suitable for oily solutions or insoluble substances
Subcutaneous	Prompt, from aqueous solution Slow and sustained, from repository preparations	Suitable for some insoluble suspensions and for implantation of solid pellets	Not suitable for large volumes Possible pain or necrosis from irritating substances
Intramuscular	Prompt, from aqueous solution Slow and sustained, from repository preparations	Suitable for moderate volumes, oily vehicles, and some irritating substances	Precluded during anticoagulant medication May interfere with interpretation of certain diagnostic tests (*e.g.*, creatine kinase)
Oral ingestion	Variable; depends upon many factors (*see* text)	Most convenient and economical; usually more safe	Requires patient cooperation Availability potentially erratic and incomplete for drugs that are poorly soluble, slowly absorbed, unstable, or extensively metabolized by the liver

* *See* text for more complete discussion and for other routes.

pass metabolism after oral administration (*see* Ridout *et al.*, 1988).

Eye. Topically applied ophthalmic drugs are used primarily for their local effects. Systemic absorption that results from drainage through the nasolacrimal canal is usually undesirable. In addition, drug that is absorbed after such drainage is not subject to first-pass hepatic elimination. Unwanted systemic pharmacological effects may occur for this reason when β-adrenergic antagonists are administered as ophthalmic drops. Local effects usually require absorption of the drug through the cornea; corneal infection or trauma may thus result in more rapid absorption. Ophthalmic delivery systems that provide prolonged duration of action (*e.g.*, suspensions and ointments) are useful additions to ophthalmic therapy. Ocular inserts, developed more recently, provide continuous delivery of low amounts of drug. Very little is lost through drainage; hence, systemic side effects are minimized.

Bioequivalence. Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration. Two pharmaceutically equivalent drug products are considered to be bioequivalent when the rates and extents of bioavailability of the active ingredient in the two products are not significantly different under suitable test conditions. In the past, dosage forms of a drug from different manufacturers and even different lots of preparations from a single manufacturer sometimes differed in their bioavailability. Such differences were seen primarily among oral dosage forms of poorly soluble, slowly absorbed drugs. They result from differences in crystal form, particle size, or other physical characteristics of the drug that are not rigidly controlled in formulation and manufacture of the preparations. These factors affect disintegration of the dosage form and dissolution of the drug and hence the rate and extent of drug absorption.

The potential nonequivalence of different drug preparations is a matter of concern. Strengthened regulatory requirements over the past few years have resulted in significantly fewer documented cases of nonequivalence between approved drug products. However, since equivalence of measured systemic concentrations of active drug and known metabolites is not necessarily proof of therapeutic equivalence, some clinicians prefer to maintain certain "fragile" patients on a single manufacturer's product. The significance of possible nonequivalence of drug preparations is further discussed in connection with drug nomenclature and the choice of drug name in writing prescription orders (*see* Appendix I).

DISTRIBUTION OF DRUGS

After a drug is absorbed or injected into the bloodstream, it may be distributed into interstitial and cellular fluids. Patterns of drug distribution reflect certain physiological factors and physicochemical properties of drugs. An initial phase of distribution may be distinguished that reflects cardiac output and regional blood flow. Heart, liver, kidney, brain, and other well perfused organs receive most of the drug during the first few minutes after absorption. Delivery of drug to muscle, most viscera, skin, and fat is slower, and these tissues may require several minutes to several hours before steady state is attained. A second phase of drug distribution may therefore be distinguished; this is also limited by blood flow, and it involves a far larger fraction of the body mass than does the first phase. Superimposed on patterns of distribution of blood flow are factors that determine the rate at which drugs diffuse into tissues. Diffusion into the interstitial compartment occurs rapidly because of the highly permeable nature of capillary endothelial membranes (except in the brain). Lipid-insoluble drugs that permeate membranes poorly are restricted in their distribution and hence in their potential sites of action. Distribution may also be limited by drug binding to plasma proteins, particularly albumin for acidic drugs and α_1-acid glycoprotein for basic drugs. An agent that is extensively and strongly bound has limited access to cellular sites of action, and it may be metabolized and eliminated slowly. Drugs may accumulate in tissues in higher concentrations than would be expected from diffusion equilibria as a result of pH gradients, binding to intracellular constituents, or partitioning into lipid.

Drug that has accumulated in a given tissue may serve as a reservoir that prolongs drug action in that same tissue or at a distant site reached through the circulation. An example that illustrates many of these factors is the use of the intravenous anesthetic thiopental, a highly lipid-soluble drug. Because blood flow to the brain is so high, the drug reaches its maximal concentration in brain within a minute after it is injected intravenously. After injection is concluded, the plasma concentration falls as thiopental diffuses into other tissues, such as muscle. The concentration of the drug in brain follows that of the plasma,

because there is little binding of the drug to brain constituents. Thus, onset of anesthesia is rapid, but so is its termination. Both are directly related to the concentration of drug in the brain. A third phase of distribution for this drug is due to the slow, blood-flow–limited uptake by fat. With administration of successive doses of thiopental, accumulation of drug takes place in fat and other tissues that can store large amounts of the compound. These can become reservoirs for the maintenance of the plasma concentration, and, therefore the brain concentration, at or above the threshold required for anesthesia. Thus, a drug that is short acting because of rapid redistribution to sites at which the agent has no pharmacological action can become long acting when these storage sites are "filled" and termination of the drug's action becomes dependent on biotransformation and excretion (*see* Benet, 1978).

Since the difference in pH between intracellular and extracellular fluids is small (7.0 vs. 7.4), this factor can result in only a relatively small concentration gradient of drug across the plasma membrane. Weak bases are concentrated slightly inside of cells, while the concentration of weak acids is slightly lower in the cells than in extracellular fluids. Lowering the pH of extracellular fluid increases the intracellular concentration of weak acids and decreases that of weak bases, provided that the intracellular pH does not also change and that the pH change does not simultaneously affect the binding, biotransformation, or excretion of the drug. Elevating the pH produces the opposite effects (*see* Figure 1–2).

Central Nervous System and Cerebrospinal Fluid. The distribution of drugs to the CNS from the bloodstream is unique, mainly in that entry of drugs into the cerebrospinal fluid and extracellular space of the CNS is restricted. The restriction is similar to that across the gastrointestinal epithelium. Endothelial cells of the brain capillaries differ from their counterparts in most tissues by the absence of intercellular pores and pinocytotic vesicles. Tight junctions predominate, and aqueous bulk flow is thus severely restricted. This is not unique to the CNS capillaries (tight junctions appear in many muscle capillaries as well). It is likely that the unique arrangement of pericapillary glial cells also contributes to the slow diffusion of organic acids and bases into the CNS. The drug molecules probably must traverse not only endothelial but also perivascular cell membranes before reaching neurons or other target cells in the CNS. Cerebral blood flow is the only limitation to permeation of the CNS by highly lipid-soluble drugs. With increasing polarity the rate of diffusion of drugs into the CNS is proportional to the lipid solubility of the nonionized species. Strongly ionized agents such as quaternary amines are normally unable to enter the CNS from the circulation.

In addition, organic ions are extruded from the cerebrospinal fluid into blood at the choroid plexus by transport processes similar to those in the renal tubule. Lipid-soluble substances leave the brain by diffusion through the capillaries and the blood–choroid plexus boundary. Drugs and endogenous metabolites, regardless of lipid solubility and molecular size, also exit with bulk flow of the cerebrospinal fluid through the arachnoid villi.

The blood–brain barrier is adaptive in that exclusion of drugs and other foreign agents such as penicillin or tubocurarine protects the CNS against severely toxic effects. However, the barrier is neither absolute nor invariable. Very large doses of penicillin may produce seizures; meningeal or encephalic inflammation increases the local permeability. Maneuvers to increase permeability of the blood–brain barrier are potentially important to enhance the efficacy of chemotherapeutic agents that are used to treat infections or tumors localized in the brain.

Drug Reservoirs. As mentioned, the body compartments in which a drug accumulates are potential reservoirs for the drug. If stored drug is in equilibrium with that in plasma and is released as the plasma concentration declines, a concentration of the drug in plasma and at its locus of action is sustained, and pharmacological effects of the drug are prolonged. However, if the reservoir for the drug has a large capacity and fills rapidly, it so alters the distribution of the drug that larger quantities of the drug are required initially to provide a therapeutically effective concentration in the target organ.

Plasma Proteins. Many drugs are bound to plasma proteins, mostly to plasma albumin for acidic drugs and to α_1-acid glycoprotein for basic drugs; binding to other plasma proteins generally occurs to a much smaller extent. The binding is usually reversible; covalent binding of reactive drugs

such as alkylating agents occurs occasionally.

The fraction of total drug in plasma that is bound is determined by the drug concentration, its affinity for the binding sites, and the number of binding sites. Simple mass-action equations are used to describe the free and bound concentrations (*see* Chapter 2). At low concentrations of drug (less than the plasma protein–binding dissociation constant), the fraction bound is a function of the concentration of binding sites and the dissociation constant. At high drug concentrations (greater than the dissociation constant), the fraction bound is a function of the number of binding sites and the drug concentration. Therefore, statements that a given drug is bound to a specified extent apply only over a limited range of concentrations. The percentage values listed in Appendix II refer only to the therapeutic range of concentrations for each drug.

Binding of a drug to plasma proteins limits its concentration in tissues and at its locus of action, since only unbound drug is in equilibrium across membranes. Binding also limits glomerular filtration of the drug, since this process does not immediately change the concentration of free drug in the plasma (water is also filtered). However, plasma protein binding does *not* generally limit renal tubular secretion or biotransformation, since these processes lower the free drug concentration, and this is rapidly followed by dissociation of the drug–protein complex. If a drug is avidly transported or metabolized and its clearance, calculated on the basis of unbound drug, exceeds organ plasma flow, binding of the drug to plasma protein may be viewed as a transport mechanism that fosters drug elimination by delivering drug to sites for elimination.

Since binding of drugs to plasma proteins is rather nonselective, many drugs with similar physicochemical characteristics can compete with each other and with endogenous substances for these binding sites. For example, displacement of unconjugated bilirubin from binding to albumin by the sulfonamides and other organic anions is known to increase the risk of bilirubin encephalopathy in the newborn, and drug toxicity has sometimes been attributed to similar competition between drugs for binding sites. Such interactions are often more complex than generally stated. Since drug displaced from plasma protein will redistribute into its full potential volume of distribution, the concentration of free drug in plasma and tissues after redistribution may be increased only slightly. The interaction may also involve altered elimination of the drug. Risk of adverse effect is greatest if the displaced drug has a limited volume of distribution, if the competition extends to the drug bound in tissues, if elimination of the drug is also reduced, or if the displacing drug is administered in high dosage by rapid intravenous injection. Competition of drugs for plasma protein-binding sites may also cause misinterpretation of measured concentrations of drugs in plasma, since most assays do not distinguish free from bound drug.

Cellular Reservoirs. Many drugs accumulate in muscle and other cells in higher concentrations than in the extracellular fluids. If the intracellular concentration is high and if the binding is reversible, the tissue involved may represent a sizable drug reservoir, particularly if the tissue represents a large fraction of body mass. For example, during long-term administration of the antimalarial agent quinacrine, the concentration of the drug in liver may be several thousand times that in plasma. Accumulation in cells may be the result of active transport or, more commonly, binding. Tissue binding of drugs usually occurs to proteins, phospholipids, or nucleoproteins and is generally reversible.

Fat as a Reservoir. Many lipid-soluble drugs are stored by physical solution in the neutral fat. In obese persons, the fat content of the body may be as high as 50%, and even in starvation it constitutes 10% of body weight; hence, fat can serve as an important reservoir for lipid-soluble drugs. For example, as much as 70% of the highly lipid-soluble barbiturate thiopental may be present in body fat 3 hours after administration. However, fat is a rather stable reservoir because it has a relatively low blood flow.

Bone. The tetracycline antibiotics (and other divalent-metal-ion chelating agents) and heavy metals may accumulate in bone by adsorption onto the bone-crystal surface and eventual incorporation into the crystal lattice. Bone can become a reservoir for the slow release of toxic agents such as lead or radium into the blood. Their effects can

thus persist long after exposure has ceased. Local destruction of the bone medulla may also lead to reduced blood flow and prolongation of the reservoir effect, since the toxic agent becomes sealed off from the circulation; this may further enhance the direct local damage to the bone. A vicious cycle results whereby the greater the exposure to the toxic agent the slower is its rate of elimination.

Transcellular Reservoirs. Drugs also cross epithelial cells and may accumulate in the transcellular fluids. The major transcellular reservoir is the gastrointestinal tract. Weak bases are passively concentrated in the stomach from the blood, because of the large pH differential between the two fluids, and some drugs are secreted in the bile in an active form or as a conjugate that can be hydrolyzed in the intestine. In these cases, and when an orally administered drug is slowly absorbed, the gastrointestinal tract serves as a drug reservoir.

Other transcellular fluids, including cerebrospinal fluid, aqueous humor, endolymph, and joint fluids, do not generally accumulate significant total amounts of drugs.

Redistribution. Termination of drug effect is usually by biotransformation and excretion, but it may also result from redistribution of the drug from its site of action into other tissues or sites. Redistribution is a factor in terminating drug effect primarily when a highly lipid-soluble drug that acts on the brain or cardiovascular system is administered rapidly by intravenous injection or by inhalation. The factors involved in redistribution of drugs have been discussed above.

Placental Transfer of Drugs. The potential transfer of drugs across the placenta is important, since drugs may cause congenital anomalies. Administered immediately before delivery, they may also have adverse effects on the neonate. Drugs cross the placenta primarily by simple diffusion. Lipid-soluble, nonionized drugs readily enter the fetal blood from the maternal circulation. Penetration is least with drugs possessing a high degree of dissociation or low lipid solubility. The view that the placenta is a barrier to drugs is inaccurate. A more appropriate approximation is that the fetus is to at least some extent exposed to essentially all drugs taken by the mother.

BIOTRANSFORMATION OF DRUGS

The physicochemical properties of drug molecules that permit rapid passage across cellular membranes during absorption and distribution also impair subsequent excretion. For example, after filtration at the renal glomerulus most lipid-soluble drugs largely escape excretion from the body because they are readily reabsorbed from the filtrate by diffusion through the renal tubular cells. Thus, the enzymatic biotransformation of drugs to more polar and less lipid-soluble metabolites enhances their excretion and reduces their volume of distribution. Such biotransformation relieves the burden of foreign chemicals and is critical for the survival of the organism. Studies of the genes that encode the enzymes of biotransformation have led to the view that they evolved millions of years ago as a mechanism for removal of natural constituents of foods, such as flavones, terpenes, steroids, and alkaloids. (For excellent summaries of drug biotransformation, *see* Goldstein *et al.*, 1974; Lee *et al.*, 1977; Jacqz *et al.*, 1986; Nebert and Gonzalez, 1987.)

Enzymes Responsible for Biotransformation. The enzyme systems responsible for the biotransformation of many drugs are located in the smooth endoplasmic reticulum of the liver (operationally designated the microsomal fraction). These enzymes also are present in other organs, such as the kidney, lung, and gastrointestinal epithelium, although in smaller quantities. Drugs absorbed from the intestine may thus be subject to the first-pass effect. This represents the combined action of hepatic and gastrointestinal epithelial enzymes, which can at times prevent effective concentrations of active drug from reaching the systemic circulation after oral administration, as discussed above.

The chemical reactions of enzymatic biotransformation are classified as either phase-I or phase-II reactions. Phase-I reactions convert the parent drug to a more polar metabolite by oxidation, reduction, or hydrolysis. The resulting metabolite may be pharmacologically inactive, less active, or occasionally more active than the parent molecule. When the metabolite itself is the active drug, the parent compound is said to be a *prodrug* (*e.g.*, enalapril). Phase-II reactions, which are also called conjugation

linization or acidification of the urine. Whether alteration of urine pH results in significant change in drug elimination depends upon the extent and persistence of the pH change and the contribution of pH-dependent passive reabsorption to total drug elimination. The effect is greatest for weak acids and bases with pK_a values in the range of urinary pH (5 to 8). However, alkalinization of urine can produce a fourfold to sixfold increase in excretion of a relatively strong acid such as salicylate when urinary pH is changed from 6.4 to 8.0. The fraction of nonionized drug would decrease from 1% to 0.04%.

Biliary and Fecal Excretion. Many metabolites of drugs formed in the liver are excreted into the intestinal tract in the bile. These metabolites may be excreted in the feces; more commonly, they are reabsorbed into the blood and ultimately excreted in the urine. Both organic anions, including glucuronides, and organic cations are actively transported into bile by carrier systems similar to those that transport these substances across the renal tubule. Both transport systems are nonselective, and ions of like charge may compete for transport. Steroids and related substances are transported into bile by a third carrier system. The effectiveness of the liver as an excretory organ for glucuronide conjugates is very much limited by their enzymatic hydrolysis after the bile is mixed with the contents of the small intestine, and the parent drug can be reabsorbed from the intestine. Thus, such compounds may undergo extensive biliary cycling with eventual excretion by the kidney.

Excretion by Other Routes. Excretion of drugs into sweat, saliva, and tears is quantitatively unimportant. Elimination by these routes is dependent mainly upon diffusion of the nonionized, lipid-soluble form of drugs through the epithelial cells of the glands and is pH dependent. Reabsorption of the nonionized drug from the primary secretion probably also occurs in the ducts of the glands, and active secretion of drugs across the ducts of the gland may also occur. Drugs excreted in the saliva enter the mouth, where they are usually swallowed. The concentration of some drugs in saliva parallels that in plasma. Saliva may therefore be a useful biological fluid in which to determine drug concentrations when it is difficult or inconvenient to obtain blood.

The same principles apply to excretion of drugs in breast milk. Since milk is more acidic than plasma, basic compounds may be slightly concentrated in this fluid, and the concentration of acidic compounds in the milk is lower than in plasma. Nonelectrolytes, such as ethanol and urea, readily enter breast milk and reach the same concentration as in plasma, independent of the pH of the milk. (*See* Atkinson *et al.*, 1988.)

Although excretion into hair and skin is also quantitatively unimportant, sensitive methods of detection of toxic metals in these tissues have forensic significance. Arsenic in Napoleon's hair, detected 150 years after administration, has raised interesting questions about how he died, and by whose hand. Mozart's manic behavior during the preparation of his last major work, the *Requiem*, may have been due to mercury poisoning; traces of the metal have been found in his hair.

CLINICAL PHARMACOKINETICS

A fundamental hypothesis of clinical pharmacokinetics is that a relationship exists between the pharmacological or toxic response to a drug and the concentration of the drug in a readily accessible site in the body (*e.g.*, blood). This hypothesis has been documented for many drugs (*see* Appendix II), although it is apparent for some drugs that no clear or simple relationship has been found between pharmacological effect and concentration in plasma. In most cases, as depicted in Figure 1–1, the concentration of drug in the systemic circulation will be related to the concentration of drug at its sites of action. The pharmacological effect that results may be the clinical effect desired, a toxic effect, or, in some cases, an effect unrelated to efficacy or toxicity. Clinical pharmacokinetics attempts to provide both a more quantitative relationship between dose and effect and the framework with which to interpret measurements of concentrations of drugs in biological fluids. The importance of pharmacokinetics in patient care rests on the improvement in efficacy that can be attained by attention to its principles when dosage regimens are chosen and modified.

The various physiological and pathophysiological variables that dictate adjustment of dosage in individual patients often do so as a result of modification of pharmacokinetic parameters. The three most important parameters are *clearance*, a measure of the body's ability to eliminate drug;

volume of distribution, a measure of the apparent space in the body available to contain the drug; and *bioavailability*, the fraction of drug absorbed as such into the systemic circulation. Of lesser importance are the *rates* of availability and distribution of the agent.

CLEARANCE

Clearance is the most important concept to be considered when a rational regimen for long-term drug administration is to be designed. The clinician usually wants to maintain steady-state concentrations of a drug within a known therapeutic range (*see* Appendix II). Assuming complete bioavailability, the steady state will be achieved when the rate of drug elimination equals the rate of drug administration:

$$\text{Dosing rate} = CL \cdot C_{ss} \quad (1)$$

where CL is clearance and C_{ss} is the steady-state concentration of drug. Thus, if the desired steady-state concentration of drug in plasma or blood is known, the rate of clearance of drug by the patient will dictate the rate at which the drug should be administered.

The concept of clearance is extremely useful in clinical pharmacokinetics because clearance of a given drug is usually constant over the range of concentrations encountered clinically. This is true because systems for elimination of drugs are not usually saturated and, thus, the *absolute* rate of elimination of the drug is essentially a linear function of its concentration in plasma. A synonymous statement is that the elimination of most drugs follows first-order kinetics—a constant *fraction* of drug is eliminated per unit of time. If mechanisms for elimination of a given drug become saturated, the kinetics become zero-order—a constant *amount* of drug is eliminated per unit of time. Under such a circumstance, clearance becomes variable. Principles of drug clearance are similar to those of renal physiology, where, for example, creatinine clearance is defined as the rate of elimination of creatinine in the urine relative to its concentration in plasma. At the simplest level, clearance of a drug is the rate of elimination by all routes normalized to the concentration of drug C in some biological fluid:

$$CL = \text{Rate of elimination}/C \quad (2)$$

It is important to note that clearance does not indicate how much drug is being removed but, rather, the volume of biological fluid such as blood or plasma that would have to be completely freed of drug to account for the elimination. Clearance is expressed as a volume per unit of time. Clearance is usually further defined as blood clearance (CL_b), plasma clearance (CL_p), or clearance based on the concentration of unbound or free drug (CL_u), depending on the concentration measured (C_b, C_p, or C_u). (For additional discussion of clearance concepts, *see* Benet *et al.*, 1984.)

Clearance by means of various organs of elimination is additive. Elimination of drug may occur as a result of processes that occur in the kidney, liver, and other organs. Division of the rate of elimination by each organ by a concentration of drug (*e.g.*, plasma concentration) will yield the respective clearance by that organ. Added together, these separate clearances will equal total systemic clearance:

$$CL_{renal} + CL_{hepatic} + CL_{other} = CL_{systemic} \quad (3)$$

Other routes of elimination could include that in saliva or sweat, partition into the gut, and metabolism at other sites.

Total systemic clearance may be determined at steady state by using equation 1. For a single dose of a drug with complete bioavailability and first-order kinetics of elimination, total systemic clearance may be determined from mass balance and the integration of equation 2 over time.

$$CL = \text{Dose}/AUC \quad (4)$$

where AUC is the total area under the curve that describes the concentration of drug in the systemic circulation as a function of time (from zero to infinity).

Examples. In Appendix II, the plasma clearance for cephalexin is reported as 4.3 $ml \cdot min^{-1} \cdot kg^{-1}$, with 91% of the drug excreted unchanged in the urine. For a 70-kg man, the total body clearance from plasma would be 300 ml/min, with renal clearance accounting for 91% of this elimination. In other words, the kidney is able to excrete cephalexin at a rate such that approximately 273 ml of

plasma would be freed of drug per minute. Because clearance is usually assumed to remain constant in a stable patient, the total rate of elimination of cephalexin will depend on the concentration of drug in the plasma (equation 2). Propranolol is cleared at a rate of 12 ml · min^{-1} · kg^{-1} (or 840 ml/min in a 70-kg man), almost exclusively by the liver. Thus, the liver is able to remove the amount of drug contained in 840 ml of plasma per minute. Of the drugs listed in Appendix II, one of the highest values of plasma clearance is that for labetalol—1750 ml/min; this value exceeds the rate of plasma (and blood) flow to the liver, the dominant organ for elimination of this drug. However, because labetalol partitions readily into red blood cells ($C_{rbc}/C_p = 1.8$), the amount of drug delivered to the excretory organ is considerably higher than suspected from measurement of its concentration in plasma. The relationship between plasma and blood clearance at steady state is given by:

$$\frac{CL_p}{CL_b} = \frac{C_b}{C_p} = 1 + H\left(\frac{C_{rbc}}{C_p} - 1\right) \tag{5}$$

One may solve for labetalol clearance from blood by substituting the red blood cell to plasma concentration ratio and the average value for the hematocrit ($H = 0.45$). Clearance of labetalol, when measured in terms of its concentration in blood, is actually 1290 ml/min, a more reasonable value. Thus the plasma clearance may assume values that are not "physiological." A drug with an extremely low concentration in plasma that is concentrated in erythrocytes (*e.g.*, mecamylamine) can show a plasma clearance of tens of liters per minute. However, if the concentration in blood is used to define clearance, the maximal clearance possible is equal to the sum of blood flows to the various organs of elimination.

As mentioned, clearance of most drugs is constant over the range of concentration in plasma or blood that is encountered in clinical settings. This means that elimination is not saturated and the rate of elimination of drug is directly proportional to its concentration (equation 2). For drugs that exhibit saturable or dose-dependent elimination, clearance will vary with the concentration of drug, often according to the following equation:

$$\text{Total plasma clearance} = V_m/(K_m + C_p) \tag{6}$$

where K_m represents the plasma concentration at which half of the maximal rate of elimination is reached (in units of mass/volume) and V_m is equal to the maximal rate of elimination (in units of mass/time). This equation is entirely analogous to the Michaelis–Menten equation for enzyme kinetics. Design of dosage regimens for such drugs is more complex (*see* below).

A further definition of clearance is useful for understanding the effects of pathological and physiological variables on drug elimination, particularly with respect to an individual organ. The rate of elimination of a drug by an individual organ can be defined in terms of the blood flow to the organ and the concentration of drug in the blood. The rate of presentation of drug to the organ is the product of blood flow (Q) and the arterial drug concentration (C_A), and the rate of exit of drug from the organ is the product of blood flow and the venous drug concentration (C_V). The difference between these rates at steady state is the rate of drug elimination:

$$\begin{aligned}\text{Rate of elimination} &= Q \cdot C_A - Q \cdot C_V \\ &= Q(C_A - C_V)\end{aligned} \tag{7}$$

Division of equation 7 by the concentration of drug that enters the organ of elimination, C_A, yields an expression for clearance of the drug by the organ in question:

$$CL_{organ} = Q\left(\frac{C_A - C_V}{C_A}\right) = Q \cdot E \tag{8}$$

The expression $(C_A - C_V)/C_A$ in equation 8 can be referred to as the extraction ratio for the drug (E).

Hepatic Clearance. The concepts developed in equation 8 have important implications for drugs that are eliminated by the liver. Consider a drug that is efficiently removed from the blood by hepatic processes—biotransformation and/or excretion of unchanged drug into the bile. In this instance, the concentration of drug in the blood leaving the liver will be low, the extraction ratio will approach unity, and the clearance of the drug from blood will become limited by hepatic blood flow. Drugs that are cleared efficiently by the liver (*e.g.*, drugs in Appendix II with clearances greater than 6 ml · min^{-1} · kg^{-1}, such as chlorpromazine, diltiazem, imipramine, lidocaine, morphine, and propranolol) are restricted in their rate of elimination not by intrahepatic processes but by the rate at which they can be transported in the blood to hepatic sites of elimination.

Additional complexities have also been considered. For example, the equations presented above do not account for drug binding to components of blood and tissues, nor do they permit an estimation of the intrinsic ability of the liver or kidney to eliminate a drug in the absence of limitations imposed by

blood flow. Extensions of the relationships of equation 8 to include expressions for protein binding and intrinsic clearance have been proposed for a number of models of hepatic elimination (*see* Roberts *et al.*, 1988). All of these models indicate that when the capacity of the eliminating organ to metabolize the drug is large in comparison with the rate of presentation of drug, the clearance will approximate the organ blood flow. In contrast, when the metabolic capability is small in comparison to the rate of drug presentation, the clearance will be proportional to the unbound fraction of drug in blood and the intrinsic clearance. Appreciation of these concepts allows one to understand a number of possibly puzzling experimental results. For example, enzyme induction or hepatic disease may change the rate of drug metabolism in an isolated hepatic microsomal enzyme system but not change clearance in the whole animal. For a drug with a high extraction ratio, clearance is limited by blood flow, and changes in the intrinsic clearance due to enzyme induction or hepatic disease should have little effect. Similarly, for drugs with high extraction ratios, changes in protein binding due to disease or competitive binding interactions should have little effect on clearance. In contrast, changes in intrinsic clearance and protein binding will affect the clearance of drugs with low extraction ratios but changes in blood flow should have little effect.

Renal Clearance. Renal clearance of a drug results in its appearance as such in the urine; changes in the pharmacokinetic properties of drugs due to renal disease may also be explained in terms of clearance concepts. However, the complications that relate to filtration, active secretion, and reabsorption must be considered. The rate of filtration of a drug depends on the volume of fluid that is filtered in the glomerulus and the unbound concentration of drug in plasma, since drug bound to protein is not filtered. The rate of secretion of drug by the kidney will depend on the binding of drug to the proteins involved in active transport relative to that bound to plasma proteins, the degree of saturation of these carriers, the rate of transfer of the drug across the tubular membrane, and the rate of delivery of the drug to the secretory site. The influences of changes in protein binding, blood flow, and the number of functional nephrons are analogous to the examples given above for hepatic elimination.

DISTRIBUTION

V lume of Distribution. Volume is a second fundamental parameter that is useful in discussing processes of drug disposition. The volume of distribution (V) relates the amount of drug in the body to the concentration of drug (C) in the blood or plasma, depending upon the fluid measured. This volume does not necessarily refer to an identifiable physiological volume, but merely to the fluid volume that would be required to contain all of the drug in the body at the same concentration as in the blood or plasma:

$$V = \text{Amount of drug in body}/C \qquad (9)$$

The plasma volume of a normal 70-kg man is 3 liters, blood volume is about 5.5 liters, extracellular fluid volume outside the plasma is 12 liters, and the volume of total body water is approximately 42 liters. However, many drugs exhibit volumes of distribution far in excess of these values. For example, if 500 μg of digoxin were in the body of a 70-kg subject, a plasma concentration of approximately 0.7 ng/ml would be observed. Dividing the amount of drug in the body by the plasma concentration yields a volume of distribution for digoxin of about 700 liters, or a value ten times greater than the total body volume of a 70-kg man. In fact, digoxin, which is relatively hydrophobic, distributes preferentially to muscle and adipose tissue and to its specific receptors, leaving a very small amount of drug in the plasma. For drugs that are extensively bound to plasma proteins but that are not bound to tissue components, the volume of distribution will approach that of the plasma volume. In contrast, certain drugs have high volumes of distribution even though most of the drug in the circulation is bound to albumin, because these drugs are also sequestered elsewhere.

The volume of distribution may vary widely depending on the pK_a of the drug, the degree of binding to plasma proteins, the partition coefficient of the drug in fat, the degree of binding to other tissues, and so forth. As might be expected, the volume of distribution for a given drug can change as a function of the patient's age, gender, disease, and body composition.

Several volume terms are commonly used to describe drug distribution, and they have been derived in a number of ways. The volume of distribution defined in equation 9 considers the body as a single homogeneous compartment (Figure 1–1). In this one-compartment model, all drug administration occurs directly into the central compartment and distribution of drug is instantaneous throughout volume (V). Clearance

of drug from this compartment occurs in a first-order fashion, as defined in equation 2; that is, the amount of drug eliminated per unit time depends on the amount (concentration) of drug in the body compartment. Figure 1–5, *A* and equation 10 describe the decline of plasma concentration with time for a drug introduced into this compartment.

$$C = (\text{Dose}/V) \cdot exp(-kt) \qquad (10)$$

where k is the rate constant for elimination of the drug from the compartment. This rate constant is inversely related to the half-life of the drug ($k = 0.693/t_{1/2}$).

For most drugs the idealized one-compartment model discussed above does not describe the entire time course of the plasma concentration. That is, certain tissue reservoirs can be distinguished from the central compartment, and the drug concentration appears to decay in a manner that can be described by multiple exponential terms (*see* Figure 1–5, *B*).

Rate of Drug Distribution. The multiple exponential decay observed for a drug that is eliminated from the body with first-order kinetics results from differences in the rates at which the drug equilibrates with tissue reservoirs. The rate of equilibration will depend upon the ratio of the perfusion of the tissue to the partition of drug into the tissue. In

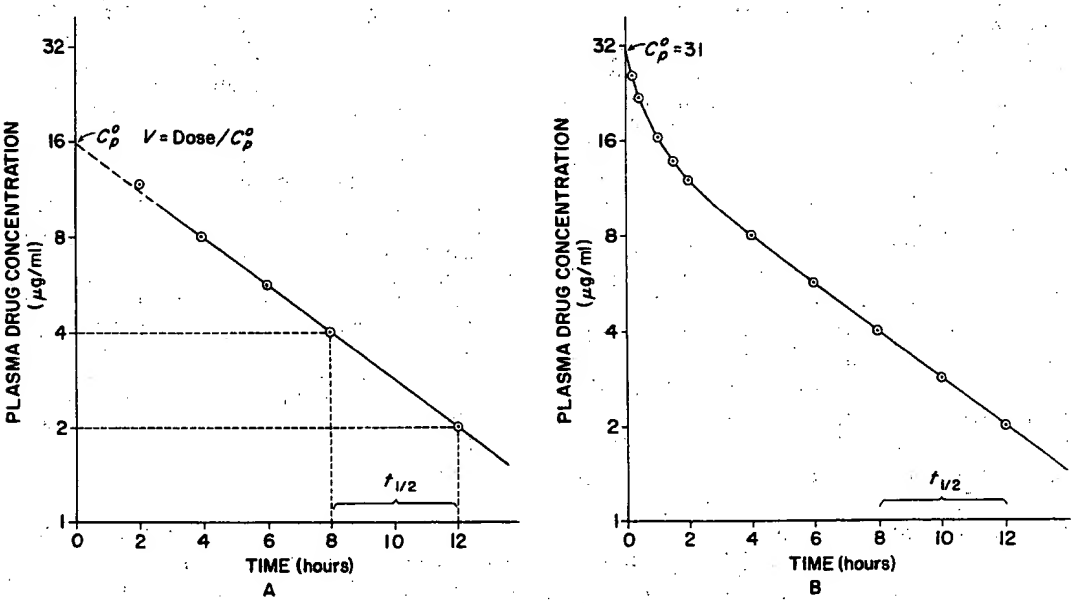

Figure 1–5. *Plasma concentration–time curves following intravenous administration of a drug (500 mg) to a 70-kg man.*

A. In this example, drug concentrations are measured in plasma 2 hours after the dose is administered. The semilogarithmic plot of plasma concentration versus time appears to indicate that the drug is eliminated from a single compartment by a first-order process (equation 10) with a half-life of 4 hours ($k = 0.693/t_{1/2} = 0.173\ hr^{-1}$). The volume of distribution (V) may be determined from the value of C_p obtained by extrapolation to $t = 0$ ($C_p^o = 16\ \mu g/ml$). Volume of distribution (equation 9) for the one-compartment model is 31.3 liters or 0.45 liter/kg ($V = \text{dose}/C_p^o$). The clearance for this drug is 92 ml/min; for a one-compartment model, $CL = k \cdot V$.

B. Sampling before 2 hours indicates that, in fact, the drug follows multiexponential kinetics. The terminal disposition half-life is 4 hours, clearance is 103 ml/min (equation 4), V_{area} is 28 liters (equation 11), and V_{ss} is 25.4 liters (equation 12). The initial or "central" distribution volume for the drug ($V_1 = \text{dose}/C_p^o$) is 16.1 liters. The example chosen indicates that multicompartment kinetics may be overlooked when sampling at early times is neglected. In this particular case, there is only a 10% error in the estimate of clearance when the multicompartment characteristics are ignored. However, for many drugs multicompartment kinetics may be observed for significant periods of time, and failure to consider the distribution phase can lead to significant errors in estimates of clearance and in predictions of the appropriate dosage.

many cases, groups of tissues with similar perfusion/partition ratios all equilibrate at essentially the same rate, such that only one apparent phase of distribution (rapid initial fall of concentration, as in Figure 1–5, *B*) is seen. It is as though the drug starts in a "central" volume, which consists of plasma and tissue reservoirs that are in rapid equilibrium with it, and distributes to a "final" volume, at which point concentrations in plasma decrease in a log-linear fashion at rate k (*see* Figure 1–5, *B*).

If the pattern or ratio of blood flows to various tissues changes within an individual or differs between individuals, rates of drug distribution to tissues will also change. However, changes in blood flow may also cause some tissues that were originally in the "central" volume to equilibrate sufficiently more slowly so as to appear only in the "final" volume. This means that central volumes will appear to vary with disease states that cause altered regional blood flow. After an intravenous bolus dose, drug concentrations in plasma may be higher in individuals with poor perfusion (*e.g.*, shock) than they would be if perfusion were better. These higher systemic concentrations may, in turn, cause higher concentrations (and greater effects) in tissues such as brain and heart whose usually high perfusion has not been reduced by the altered hemodynamic state. Thus, the effect of a drug at various sites of action can be variable, depending on perfusion of these sites.

Multicompartment Volume Terms. Two different terms have been used to describe the volume of distribution for drugs that follow multiple exponential decay. The first, designated V_{area}, is calculated as the ratio of clearance to the rate of decline of concentration during the elimination (final) phase of the logarithmic concentration versus time curve:

$$V_{area} = \frac{CL}{k} = \frac{\text{Dose}}{k \cdot AUC} \qquad (11)$$

The calculation of this parameter is straightforward, and the volume term may be determined after administration of drug by intravenous or enteral routes (where the dose used must be corrected for bioavailability). However, another multicompartment volume of distribution may be more useful, especially when the effect of disease states on pharmacokinetics is to be determined. The volume of distribution at steady state (V_{ss}) represents the volume in which a drug would appear to be distributed during steady state if the drug existed throughout that volume at the same concentration as that in the measured fluid (plasma or blood). This volume can be determined by the use of areas, as described by Benet and Galeazzi (1979):

$$V_{ss} = (\text{Dose}_{iv})(AUMC)/AUC^2 \qquad (12)$$

where $AUMC$ is the area under the first moment of the curve that describes the time course of the plasma or blood concentration, that is, the area under the curve of the product of time t and plasma or blood concentration C over the time span zero to infinity.

Although V_{area} is a convenient and easily calculated parameter, it varies when the rate constant for drug elimination changes, even when there has been no change in the distribution space. This is because the terminal rate of decline of the concentration of drug in blood or plasma depends not only on clearance but also on the rates of distribution of drug between the central and final volumes. V_{ss} does not suffer from this disadvantage (*see* Benet *et al.*, 1984).

HALF-LIFE

The half-life ($t_{1/2}$) is the time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%. For the simplest case, the one-compartment model (Figure 1–5, *A*), half-life may be determined readily and used to make decisions about drug dosage. However, as indicated in Figure 1–5, *B*, drug concentrations in plasma often follow a multiexponential pattern of decline; two or more half-life terms may thus be calculated.

In the past, the half-life that was usually reported corresponded to the terminal log-linear phase of elimination. However, as greater analytical sensitivity has been achieved, the lower concentrations measured appeared to yield longer and longer terminal half-lives. For example, a terminal half-life of 53 hours is observed for gentamicin (versus the 2-to-3-hour value in Appendix II), and biliary cycling is probably responsible for the 120-hour terminal value for indomethacin (as compared with the 2.4-hour half-life listed in Appendix II). The relevance of a particular half-life may be defined in terms of the fraction of the clearance and volume of distribution that is related to each half-life and whether plasma concentrations or amounts of drug in the body are best related to measures of response (*see* Benet, 1984). The single half-life values given for each drug in Appendix II are chosen to represent the most clinically relevant half-life.

Early studies of pharmacokinetic properties of drugs in disease were compromised by their reliance on half-life as the sole measure of alterations of drug disposition. Only recently has it been appreciated that half-life is a derived parameter that changes as a function of both clearance and volume of distribution. A useful approximate relationship between the clinically relevant half-life, clearance, and volume of distribution is given by:

$$t_{1/2} \cong 0.693 \cdot V/CL \qquad (13)$$

Clearance is the measure of the body's ability to eliminate a drug. However, the organs of elimination can only clear drug from the blood or plasma with which they are in direct contact. As clearance decreases, due to a disease process, for example, half-life would be expected to increase. However, this reciprocal relationship is exact only when the disease does not change the volume of distribution. For example, the half-life of diazepam increases with increasing age; however, it is not clearance that changes as a function of age, but the volume of distribution (Klotz *et al.*, 1975). Similarly, changes in protein binding of the drug may affect its clearance as well as its volume of distribution, leading to unpredictable changes in half-life as a function of disease. The half-life of tolbutamide, for example, decreases in patients with acute viral hepatitis, exactly the opposite from what one might expect. The disease appears to modify protein binding in both plasma and tissues, causing no change in volume of distribution but an increase in total clearance because higher concentrations of free drug are present (Williams *et al.*, 1977).

Although it can be a poor index of drug elimination, half-life does provide a good indication of the time required to reach steady state after a dosage regimen is initiated (*i.e.*, four half-lives to reach approximately 94% of a new steady state), the time for a drug to be removed from the body, and a means to estimate the appropriate dosing interval (*see* below).

Steady State. Equation 1 indicates that a steady-state concentration will eventually be achieved when a drug is administered at a constant rate. At this point, drug elimination (the product of clearance and concentration; equation 2) will equal the rate of drug availability. This concept also extends to intermittent dosage (*e.g.*, 250 mg of drug every 8 hours). During each interdose interval, the concentration of drug rises and falls. At steady state, the entire cycle is repeated identically in each interval. Equation 1 still applies for intermittent dosing, but it now describes the average drug concentration during an interdose interval. Steady-state dosing is illustrated in Figure 1–6.

Extent and Rate of Availability

Bioavailability. It is important to distinguish between the rate and extent of drug absorption and the amount that ultimately reaches the systemic circulation, as discussed above. The amount of the drug that reaches the systemic circulation can be expressed as a fraction of the dose F, which is often called bioavailability. Reasons for incomplete absorption have been discussed above. Also, as noted previously, if the drug is metabolized in the liver or excreted in bile, some of the active drug absorbed from the gastrointestinal tract will be inactivated by the liver before it can reach the general circulation and be distributed to its sites of action.

Knowing the extraction ratio (E) for a drug across the liver (*see* equation 8), it is possible to predict the maximum oral availability (F_{max}), assuming hepatic elimination follows first-order processes:

$$F_{max} = 1 - E = 1 - (CL_{hepatic}/Q_{hepatic}) \quad (14)$$

Thus, if the hepatic blood clearance for the drug is large relative to hepatic blood flow, the extent of availability will be low when it is given orally (*e.g.*, lidocaine). This decrease in availability is a function of the physiological site from which absorption takes place, and no modification of dosage form will improve the availability under conditions of linear kinetics.

When drugs are administered by a route that is subject to first-pass loss, the equations presented previously that contain the terms *dose* or *dosing rate* (equations 1, 4, 10, and 11) must also include the bioavailability term F such that the available dose or dosing rate is used. For example, equation 1 is modified to:

$$F \cdot \text{Dosing rate} = CL \cdot C_{ss} \quad (15)$$

Rate of Absorption. Although the rate of drug absorption does not, in general, influence the average steady-state concentration of the drug in plasma, it may still influence drug therapy. If a drug is absorbed very rapidly (*e.g.*, a dose given as an intravenous bolus) and has a small central vol-

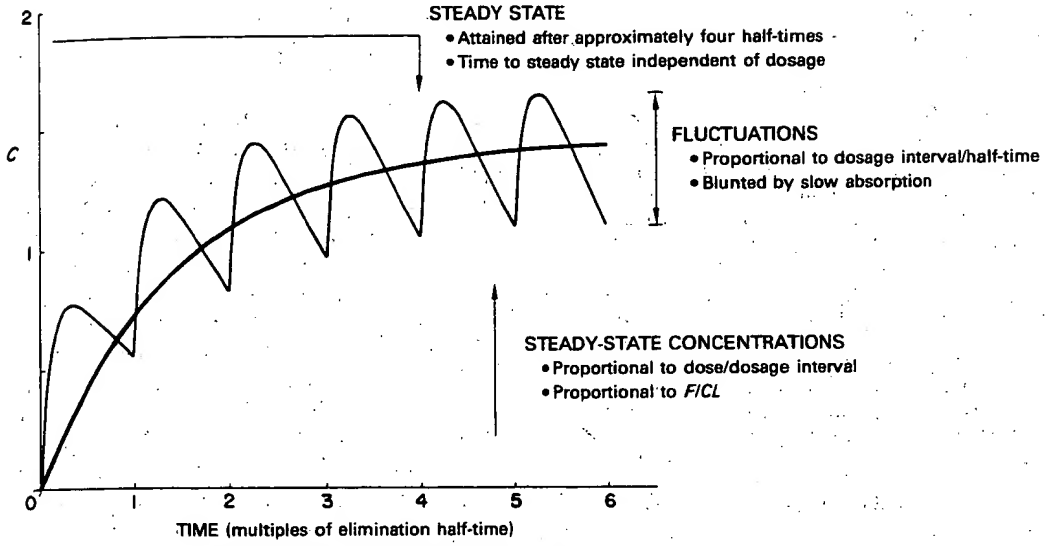

Figure 1–6. *Fundamental pharmacokinetic relationships for repeated administration of drugs.*

Light line is the pattern of drug accumulation during repeated administration of a drug at intervals equal to its elimination half-time, when drug absorption is ten times as rapid as elimination. As the relative rate of absorption increases, the concentration maxima approach 2 and the minima approach 1 during the steady state. Heavy line depicts the pattern during administration of equivalent dosage by continuous intravenous infusion. Curves are based upon the one-compartment model.

Average concentration ($\bar{C}_{ss}$) when the steady state is attained during intermittent drug administration:

$$\bar{C}_{ss} = \frac{F \cdot \text{dose}}{CL \cdot T}$$

where F = fractional bioavailability of the dose and T = dosage interval (time). By substitution of infusion rate for $F \cdot \text{dose}/T$, the formula is equivalent to equation 1 and provides the concentration maintained at steady state during continuous intravenous infusion.

ume, the concentration of drug will be high initially. It will then fall as the drug is distributed to its final (larger) volume (*see* Figure 1–5, *B*). If the same drug is absorbed more slowly (*e.g.*, by slow infusion), it will be distributed while it is being given, and peak concentrations will be lower and will occur later. A given drug may act to produce both desirable and undesirable effects at several sites in the body, and the rates of distribution of drug to these sites may not be the same. The relative intensities of these different effects of a drug may thus vary transiently when its rate of administration is changed.

NONLINEAR PHARMACOKINETICS

Nonlinearity in pharmacokinetics (*i.e.*, changes in such parameters as clearance, volume of distribution, and half-life as a function of dose or concentration of drug) is usually due to saturation of protein binding, hepatic metabolism, or active renal transport of the drug.

Saturable Protein Binding. As the molar concentration of drug increases, the unbound fraction must eventually also increase (as all binding sites become saturated). This usually occurs only when drug concentrations in plasma are in the range of tens to hundreds of micrograms per milliliter. For a drug that is metabolized by the liver with a low extraction ratio, saturation of plasma protein binding will cause both V and clearance to increase as drug concentrations increase; half-life may thus remain constant (*see* equation 13). For such a drug, C_{ss} will not increase linearly as the rate of drug administration is increased. For drugs that are cleared with high extraction ratios, C_{ss} can remain linearly proportional to the rate of drug administration. In this case, hepatic clearance would not change, and the increase in V would increase the half-time of disap-

pearance by reducing the fraction of the total drug in the body that is delivered to the liver per unit time. Most drugs fall between these two extremes, and the effects of nonlinear protein binding may be difficult to predict.

Saturable Metabolism. In this situation, the Michaelis–Menten equation (equation 6) usually describes the nonlinearity. All active processes are undoubtedly saturable, but they will appear to be linear if values of drug concentrations encountered in practice are much less than K_m. When they exceed K_m, nonlinear kinetics is observed. The major consequences of saturation of metabolism are the opposite of those for saturation of protein binding. When both conditions are present simultaneously, they may virtually cancel each others' effects, and surprisingly linear kinetics may result; this occurs over a certain range of concentrations for salicylic acid.

Saturable metabolism causes first-pass metabolism to be less than expected (higher F), and there is a greater fractional increase in C_{ss} than the corresponding fractional increase in the rate of drug administration. The latter can be seen most easily by substituting equation 6 into equation 1 and solving for the steady-state concentration:

$$C_{ss} = \frac{\text{Dosing rate} \cdot K_m}{V_m - \text{Dosing rate}} \qquad (16)$$

As the dosing rate approaches the maximal elimination rate (V_m), the denominator of equation 16 approaches zero and C_{ss} increases disproportionately. Fortunately, saturation of metabolism should have no effect on the volume of distribution; thus, as clearance decreases, the apparent half-life for elimination increases and the approach to the (disproportionate) new steady state is slow. However, the concept of "four half-lives to steady state" is not applicable for drugs with nonlinear metabolism in the usual range of clinical concentrations.

Phenytoin provides an example of a drug for which metabolism becomes saturated in the therapeutic range of concentrations (*see* Appendix II). K_m is typically near the lower end of the therapeutic range (K_m = 5 to 10 mg per liter). For some individuals, especially children, K_m may be as low as 1 mg per liter. If, for such an individual, the target concentration is 15 mg per liter and this is attained at a dosing rate of 300 mg per day, then, from equation 16, V_m equals 320 mg per day. For such a patient, a dose 10% less than optimal (*i.e.*, 270 mg per day) will produce a C_{ss} of 5 mg per liter, well below the desired value. In contrast, a dose 10% greater than optimal (330 mg per day) will exceed metabolic capacity (by 10 mg per day) and cause a long and slow but unending climb in concentration until toxicity occurs. Dosage cannot be controlled so precisely (less than 10% error). Therefore, for those patients in whom the target concentration for phenytoin is more than tenfold greater than the K_m, alternating inefficacious therapy and toxicity is almost unavoidable.

Design and Optimization of Dosage Regimens

When long-term therapy is initiated, a pharmacodynamic question must be asked: What degree of drug effect is desired and achievable? If some effect of the drug is easily measured (*e.g.*, blood pressure), it can be used to guide dosage, and a trial-and-error approach to optimal dosage is both practical and sensible. Even in this ideal case, certain quantitative issues arise, such as how often to change dosage and by how much. These can usually be settled with simple rules of thumb based on the principles discussed (*e.g.*, change dosage by no more than 50% and no more often than every three to four half-lives). Alternatively, some drugs have very little dose-related toxicity, and maximum efficacy is usually desired. For these drugs, doses well in excess of the average required will both ensure efficacy (if this is possible) and prolong drug action. Such a "maximal dose" strategy is typically used for penicillins and most β-adrenergic blocking agents.

Target Level. For some drugs, the effects are difficult to measure (or the drug is given for prophylaxis), toxicity and lack of efficacy are both potential dangers, and/or the therapeutic index is narrow. In these circumstances doses must be titrated carefully, and a target-level strategy is reasonable. A desired (target) steady-state concentration of the drug (usually in plasma) is chosen, and a dosage is computed that is expected to achieve this value. Drug concentrations are subsequently measured, and dosage is adjusted if necessary to approximate the target more closely (*see also* Chapter 4).

To apply the target-level strategy, the therapeutic objective must be defined in terms of a desirable range for the C_{ss}, often called the therapeutic range. For drugs for which this can be done, such as theophylline and digoxin, the lower limit of the therapeutic range appears to be approximately equal to the drug concentration that produces about half of the greatest possible therapeutic effect. The upper limit of the therapeutic range (for drugs with such a limit) is fixed by toxicity, not by efficacy.

In general, the upper limit of the therapeutic range is such that no more than 5 to 10% of patients will experience a toxic effect. For some drugs, this may mean that the upper limit of the range is no more than twice the lower limit. Of course, these figures can be highly variable, and some patients may benefit greatly from drug concentrations that exceed the therapeutic range while others may suffer significant toxicity at much lower values. Barring more specific information, however, the target is usually chosen as the center of the therapeutic range.

Maintenance Dose. In most clinical situations, drugs are administered in a series of repetitive doses or as a continuous infusion in order to maintain a steady-state concentration of drug in plasma within a given therapeutic range. Thus, calculation of the appropriate maintenance dosage is a primary goal. To maintain the chosen steady-state or target concentration, the rate of drug administration is adjusted such that the rate of input equals the rate of loss. This relationship was defined previously in equations 1 and 15 and is expressed here in terms of the desired target concentration:

$$\text{Dosing rate} = \text{Target} \cdot CL/F \tag{17}$$

If the clinician chooses the desired concentration of drug in plasma and knows the clearance and availability for that drug in a particular patient, the appropriate dose and dosing interval can be calculated.

Example. A steady-state plasma concentration of theophylline of 15 mg per liter is desired to relieve acute bronchial asthma in a 68-kg patient. If the patient does not smoke and is otherwise normal except for the asthmatic condition, one can use the mean clearance given in Appendix II, that is, 0.65 ml · min^{-1} · kg^{-1}. Because the drug is to be given as an intravenous infusion, $F = 1$:

$$\begin{aligned}\text{Dosing rate} &= \text{Target} \cdot CL/F \\ &= 15\ \mu g/ml \cdot 0.65\ ml \cdot min^{-1} \cdot kg^{-1} \\ &= 9.75\ \mu g \cdot min^{-1} \cdot kg^{-1} \\ &= 40\ mg/hr \text{ for a 68-kg patient}\end{aligned}$$

Since almost all intravenous preparations of theophylline are available as the ethylenediamine salt (aminophylline), which contains 85% theophylline, the infusion rate will be 47 mg per hour of aminophylline [(40 mg per hour)/(0.85)].

Dosing Interval for Intermittent Dosage. In general, marked fluctuations in drug concentrations between doses are not beneficial. If absorption and distribution were instantaneous, fluctuation of drug concentrations between doses would be governed entirely by the drug's elimination half-life. If the dosing interval (T) was chosen to be equal to the half-life, then the total fluctuation would be twofold; this is usually a tolerable variation.

Pharmacodynamic considerations modify this. If a drug is relatively nontoxic, such that concentrations many times that necessary for therapy can easily be tolerated, the maximal dose strategy can be used and the dosing interval can be much longer than the elimination half-life (for convenience). The half-life of penicillin G is less than 1 hour, but it is often given in very large doses every 6 or 12 hours.

For some drugs with a narrow therapeutic range, it may be important to estimate the maximal and minimal concentrations that will occur for a particular dosing interval. The minimal steady-state concentration $C_{ss,min}$ may be reasonably determined by the use of equation 18:

$$C_{ss,min} = \frac{F \cdot \text{dose}/V_{ss}}{1 - exp(-kT)} \cdot exp(-kT) \tag{18}$$

where k equals 0.693 divided by the clinically relevant plasma half-life and T is the dosing interval. The term $exp(-kT)$ is, in fact, the fraction of the last dose (corrected for bioavailability) that remains in the body at the end of a dosing interval.

For drugs that follow multiexponential kinetics and that are administered orally, the estimation of the maximal steady-state concentration $C_{ss,max}$ involves a complicated set of exponential constants for distribution and absorption. If these terms are ignored for multiple oral dosing, one may easily predict a maximal steady-state concentration by omitting the $exp(-kT)$ term in the numerator of equation 18 (*see* equation 19, below). Because of the approximation, the predicted maximal concentration from equation 19 will be greater than that actually observed.

Example. When the acute asthmatic attack in the patient discussed above is relieved, the clinician might want to maintain the plasma concentration of theophylline at 15 mg per liter, with oral dosage at intervals of 6, 8, or 12 hours. The correct rate of drug administration, independent of consideration of the dosing interval, is 40 mg per hour for this patient, as calculated above, since the availability of theophylline from an oral dose is 100%. Thus, the appropriate intermittent doses would be 240 mg every 6 hours, 320 mg every 8 hours, or 480 mg every 12 hours. All of these regimens would yield the same average concentration of 15 mg per liter, but different maximal and minimal concentrations would obtain. For a 12-hour dosing interval, the following maximal and minimal concentrations would be predicted:

$$C_{ss,max} = \frac{F \cdot \text{dose}/V_{ss}}{1 - exp(-kT)} = \frac{480 \text{ mg}/34 \text{ liters}}{0.65} = 22 \text{ mg/liter} \quad (19)$$

$$C_{ss,min} = C_{ss,max} \cdot exp(-kT) = (21.7 \text{ mg/liter}) \cdot (0.35) = 7.6 \text{ mg/liter} \quad (20)$$

The calculations in equations 19 and 20 were performed assuming oral doses of 480 mg every 12 hours of a drug with a half-life of 8 hours (k = 0.693/8 hr = 0.0866 hr^{-1}), a volume of distribution of 0.5 liter/kg (V_{ss} = 34 liters for a 68-kg patient), and an oral availability of 1. Since the predicted minimal concentration, 7.6 mg per liter, falls below the suggested effective concentration and the predicted maximal concentration is above that suggested to avoid toxicity (*see* Appendix II), the choice of a 12-hour dosing interval is probably inappropriate. A more appropriate choice would be 320 mg every 8 hours or 240 mg every 6 hours; for T = 6 hr, $C_{ss,max}$ = 17 mg per liter; $C_{ss,min}$ = 10 mg per liter. Of course the clinician must balance the problem of compliance with regimens that involve frequent dosage against the problem of periods when the patient may be subjected to concentrations of the drug that could be too high or too low.

Loading Dose. The "loading dose" is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly. The appropriate magnitude for the loading dose is:

$$\text{Loading dose} = \text{Target } C_p \cdot V_{ss}/F \quad (21)$$

A loading dose may be desirable if the time required to attain steady state by the administration of drug at a constant rate (four elimination half-lives) is long relative to the temporal demands of the condition being treated. For example, the half-life of lidocaine is usually more than 1 hour. Arrhythmias encountered after myocardial infarction may obviously be life threatening, and one cannot wait 4 to 6 hours to achieve a therapeutic concentration of lidocaine by infusion of the drug at the rate required to maintain this concentration. Hence, use of a loading dose of lidocaine in the coronary care unit is standard.

The use of a loading dose also has significant disadvantages. First, the particularly sensitive individual may be exposed abruptly to a toxic concentration of a drug. Moreover, if the drug involved has a long half-life, it will take a long time for the concentration to fall if the level achieved was excessive. Loading doses tend to be large, and they are often given parenterally and rapidly; this can be particularly dangerous if toxic effects occur as a result of actions of the drug at sites that are in rapid equilibrium with plasma.

Individualizing Dosage. To design a rational dosage regimen, the clinician must know F, CL, V_{ss}, and $t_{1/2}$, and have some knowledge about rates of absorption and distribution of the drug. Moreover, one must judge what variations in these parameters might be expected in a particular patient. Usual values for the important parameters and appropriate adjustments that may be necessitated by disease or other factors are presented in Appendix II. There is, however, unpredictable variation between normal individuals; for many drugs, one standard deviation in the values observed for F, CL, and V_{ss} is about 20%, 50%, and 30%, respectively. This means that 95% of the time the C_{ss} that is achieved will be between 35% and 270% of the target; this is an unacceptably wide range for a drug with a low therapeutic index. If values of C_p are measured, one can estimate values of F, CL, and V_{ss} directly, and this permits more precise adjustment of a dosage regimen. Such measurement and adjustment are appropriate for many drugs with low therapeutic indices (*e.g.*, cardiac glycosides, antiarrhythmic agents, anticonvulsants, theophylline, and others).

THERAPEUTIC DRUG MONITORING

The major use of measured concentrations of drugs (at steady state) is to refine the estimate of CL/F for the patient being treated (using equation 15 as rearranged below):

$$CL/F \text{ (patient)} = \text{Dosing rate}/C_{ss} \text{ (measured)} \quad (22)$$

The new estimate of CL/F can be used in equation 17 to adjust the maintenance dose to achieve the desired target concentration.

Certain practical details and pitfalls related to therapeutic drug monitoring should be kept in mind. The first of these concerns the time of sam-

pling for measurement of the drug concentration. If intermittent dosing is used, when during a dosing interval should samples be taken? It is necessary to distinguish between two possible uses of measured drug concentrations in order to understand the possible answers. A concentration of drug measured in a sample taken at virtually any time during the dosing interval will provide information that may aid in the assessment of drug toxicity. This is one type of therapeutic drug monitoring. It should be stressed, however, that such use of a measured concentration of drug is fraught with difficulties because of interindividual variability in sensitivity to the drug. When there is a question of toxicity, the drug concentration can be no more than just one of many items that serve to inform the clinician.

Changes in the effects of drugs may be delayed relative to changes in plasma concentration because of a slow rate of distribution or pharmacodynamic factors. Concentrations of digoxin, for example, regularly exceed 2 ng/ml (a potentially toxic value) shortly after an oral dose, yet these peak concentrations do not cause toxicity; indeed, they occur well before peak effects. Thus, concentrations of drugs in samples obtained shortly after administration can be uninformative or even misleading.

When concentrations of drugs are used for purposes of adjusting dosage regimens, samples obtained shortly after administration of a dose are almost invariably misleading. The point of sampling during supposed steady state is to modify one's estimate of CL/F and thus one's choice of dosage. Early postabsorptive concentrations do not reflect clearance; they are determined primarily by the rate of absorption, the central (rather than the steady-state) volume of distribution, and the rate of distribution, all of which are pharmacokinetic features of virtually no relevance in choosing the long-term maintenance dosage. When the goal of measurement is adjustment of dosage, the sample should be taken well after the previous dose—as a rule of thumb just before the next planned dose, when the concentration is at its minimum. There is an exception to this approach: some drugs are nearly completely eliminated between doses and act only during the initial portion of each dosing interval. If, for such drugs, it is questionable whether efficacious concentrations are being achieved, a sample taken shortly after a dose may be helpful. Yet, if another concern is that low clearance (as in renal failure) may cause accumulation of drug, concentrations measured just before the next dose will reveal such accumulation and are considerably more useful for this purpose than is knowledge of the maximal concentration. For such drugs, determination of both maximal and minimal concentrations is thus recommended.

A second important aspect of the timing of sampling is its relationship to the beginning of the maintenance dosage regimen. When constant dosage is given, steady state is reached only after four half-lives have passed. If a sample is obtained too soon after dosage is begun, it will not accurately reflect clearance. Yet, for toxic drugs, if one waits until steady state is ensured, the damage may have been done. Some simple guidelines can be offered. When it is important to maintain careful control of concentrations, one may take the first sample after two half-lives (as calculated and expected for the patient), assuming no loading dose has been given. If the concentration already exceeds 90% of the eventual expected mean steady-state concentration, the dosage rate should be halved, another sample obtained in another two (supposed) half-lives, and the dosage halved again if this sample exceeds the target. If the first concentration is not too high, one proceeds with the initial rate of dosage; even if the concentration is lower than expected, one can usually await the attainment of steady state in another two estimated half-lives and then proceed to adjust dosage as described above.

If dosage is intermittent, there is a third concern with the time at which samples are obtained for determination of drug concentrations. If the sample has been obtained just prior to the next dose, as recommended, concentration will be a minimal value, not the mean. However, as discussed above, the estimated mean concentration may be calculated by using equation 15.

If a drug follows first-order kinetics, the average, minimum, and maximum concentrations at steady state are linearly related to dose and dosing rate (*see* equations 15, 18, and 19). Therefore, the ratio between the measured and the desired concentrations can be used to adjust the dose:

$$\frac{C_{ss}(\text{measured})}{C_{ss}(\text{desired})} = \frac{\text{Dose(previous)}}{\text{Dose(new)}} \tag{23}$$

Finally, for some drugs that are particularly difficult to manage, computer programs may be useful for the design of dosage regimens. Such programs, which take into account measured drug concentrations and individual factors such as those listed in Appendix II, are becoming increasingly available (see Sheiner *et al.*, 1972; Vozeh and Steimer, 1985).

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APPENDIX D

Transclean Corp. v. Bridgewood Serv.,
290 F.3d 1364 (Fed. Cir. 2002)

possible."). Thus, for example, in a case arising under the WPA where the government employee makes non-frivolous allegations that he was terminated in retaliation for making protected disclosures, an administrative judge could properly hold an initial hearing limited to the question of whether the employee would have been properly terminated absent the disclosures, such as where the employee's attendance record was clearly unsatisfactory. If after such a limited merits hearing the Board concluded that the employee would have been properly terminated absent the protected disclosures, the employee's claim could be rejected on the merits, subject to right of appeal to the full Board and to this court. This authority is akin to that granted district court judges by Federal Rule of Civil Procedure 16(c)(14), which allows district court judges to govern the order of proof presented at trial, and to allow separate trials of particular issues.[5]

CONCLUSION

[11] We reiterate that non-frivolous jurisdictional allegations supported by affidavits or other evidence confer Board jurisdiction. The truth of such allegations is tested in a hearing in which appellant must prove the allegations by preponderant evidence. These hearings are not "jurisdictional" hearings—they are hearings on the merits. Because we find that appellant did not waive his right to a hearing on the merits, we vacate and remand for further proceedings not inconsistent with this opinion. We do not reach the question whether the Board's finding of involuntariness was supported by substantial evidence.

COSTS

No costs.

VACATED AND REMANDED.

TRANSCLEAN CORPORATION, James P. Viken, Jon A. Lang, and Donald E. Johnson, Plaintiffs–Appellants,

v.

BRIDGEWOOD SERVICES, INC., Defendant/Cross–Appellant.

Nos. 01–1268, 01–1269.

United States Court of Appeals, Federal Circuit.

Decided: May 21, 2002.

Rehearing Denied: July 2, 2002.

Assignee of patent for automat transmission fluid changing device sue competitor for patent infringement, trad mark infringement, and false advertisin The United States District Court for tl District of Minnesota, Raymond L. Eric son, United States Magistrate Judge, e tered judgment in favor of competitor trademark infringement claim, F.Supp.2d 1045, entered judgment in fav of assignee on patent infringement a false advertising claims, but denied its m tion for enhanced damages and attorn fees, 134 F.Supp.2d 1049. Both parties a pealed. The Court of Appeals, Lourie, C cuit Judge, held that: (1) patent was

5. Rule 16(c)(14) states in pertinent part:

> At any conference under this rule consideration may be given, and the court may take appropriate action, with respect to ... an order directing a party or parties to present evidence early in the trial with respect to a manageable issue that could, on the dence, be the basis for a judgment a matter of law under Rule 50(a) or a ju ment on partial pretrial findings under R 52(c).

Fed.R.Civ.P. 16(c)(14).

anticipated by two prior art patents; (2) precluding competitor from arguing noninfringement as discovery sanction was not abuse of discretion; (3) assignee was not entitled to reasonable royalty based upon competitor's proceeds from sale of its business; (4) award of enhanced damages or attorney fees was not warranted; and (5) assignee did not sufficiently use its unregistered marks in commerce to support infringement claim.

Affirmed in part and vacated in part.

Clevenger, Circuit Judge, filed opinion dissenting in part.

1. **Patents ⇐65, 72(1)**

Determination that a patent is invalid as being anticipated requires a finding that each and every limitation is found either expressly or inherently in a single prior art reference; to anticipate, the reference must also enable one of skill in the art to make and use the claimed invention. 35 U.S.C.A. § 102.

2. **Patents ⇐112.5**

Because a patent issued by the Patent and Trademark Office (PTO) is presumed to be valid, evidentiary burden to show facts supporting a conclusion of invalidity is clear and convincing evidence. 35 U.S.C.A. § 282.

3. **Patents ⇐226.6**

Determination of patent infringement requires a two-step analysis: first, the court determines the scope and meaning of the patent claims asserted; second, the properly construed claims are compared to the allegedly infringing device.

4. **Patents ⇐314(5), 324.5**

Claim construction in patent infringement case is an issue of law that Court of Appeals reviews de novo.

5. **Patents ⇐226.6, 314(5)**

Comparison of patent claim to accused device requires a determination that every claim limitation or its equivalent be found in the accused device; those determinations are questions of fact.

6. **Patents ⇐319(1)**

Choice of methodology for calculating damages is within the discretion of the district court in patent infringement case.

7. **Patents ⇐312(1.7), 324.55(1)**

Patent owner bears burden of proving by preponderance of the evidence the quantum of damages, an issue of fact for which Court of Appeals reviews the jury's decision for substantial evidence.

8. **Courts ⇐96(5, 7)**

A decision to sanction a litigant for discovery violations is one that is not unique to patent law, and Court of Appeals for the Federal Circuit therefore applies regional circuit law to that issue. Fed. Rules Civ.Proc.Rule 37, 28 U.S.C.A.

9. **Patents ⇐101(4)**

Phrase "equalizing the fluid flow" in patent for automatic transmission fluid changing apparatus referred to a rate, not just a volume; specification referred to equalization of flow rates, and patent described problems that could occur in prior art when input flow rate of added fluid did not match the output flow rate of used fluid.

10. **Patents ⇐65**

To anticipate a patent claim reciting a means-plus-function limitation, the anticipatory reference must disclose the recited function identically. 35 U.S.C.A. § 112.

11. **Patents ⇐66(1.9)**

Patent for automatic transmission fluid changing apparatus which contained "means for equalizing fluid flow" means-plus-function limitation was not anticipated by two prior art patents; prior art patents disclosed equalization of fluid amount, but

not necessarily fluid flow rates. 35 U.S.C.A. § 112.

12. Patents ⇐65

Anticipation of patent by inherent disclosure is appropriate only when reference discloses prior art that must necessarily include the unstated limitation. 35 U.S.C.A. § 102.

13. Patents ⇐292.1(4)

Precluding assignee's competitor from arguing noninfringement as discovery sanction for competitor's failure to answer interrogatory seeking its bases for arguing noninfringement was not abuse of discretion in action for infringement of patent for automatic transmission fluid changing apparatus. Fed.Rules Civ.Proc.Rule 37, 28 U.S.C.A.

14. Patents ⇐101(2)

Phrase "exhibiting resilient characteristics" in patent for automatic transmission fluid changing apparatus meant "retuning to an original shape after being deformed" or "returning to its original position after being compressed."

15. Patents ⇐318(4.1)

Patent assignee was not entitled to reasonable royalty based upon infringer's proceeds from sale of its business, although infringer's sole source of revenue was infringing product; portions of sales price consisting of goodwill was not sale of infringing goods that could form base for determination of a reasonable royalty.

16. Patents ⇐319(3)

Determination that patent assignee's competitor had willfully infringed patent for automatic transmission fluid changing apparatus did not require award of enhanced damages in infringement action. 35 U.S.C.A. § 284.

17. Patents ⇐319(3)

Enhancement of damages in patent infringement case involves fact-finder determining that the infringer engaged in culpable conduct and the court exercising its discretion to determine whether and to what extent to enhance the damages. 35 U.S.C.A. § 284.

18. Patents ⇐325.11(2.1)

Determination that enhanced damages were not warranted despite willful patent infringement by patent assignee's competitor supported implicit conclusion that case was not "exceptional," within meaning of patent attorney fee statute. 35 U.S.C.A. § 285.

See publication Words and Phrases for other judicial constructions and definitions.

19. Patents ⇐325.11(5)

Generally, district court must normally explain why it decides that a case is not exceptional under patent attorney fee statute when a factual finding of willful infringement has been established and, if exceptional, why it decides not to award attorney fees. 35 U.S.C.A. § 285.

20. Trade Regulation ⇐862

Purpose of Minnesota's private attorney general statute is to encourage private parties to police unlawful trade practices affecting the public interest. M.S.A. § 8.31.

21. Attorney and Client ⇐92

Patent assignee was not entitled to award of attorney fees under Minnesota's private attorney general statute for its successful claim that competitor engaged in false advertising of its automatic transmission fluid changing product; assignee's own use of arguably false advertising and tolerance of same advertising by its licensee erased any public benefit from its successful action against competitor. M.S.A. § 8.31.

22. Trade Regulation ⇐67

Trademark holder's use of unregistered trademarks "total fluid exchange"

and "total fluid x-change" on its automatic transmission fluid change products and its documents was insufficient use of the marks in commerce to support trademark infringement claim; use of marks on documents did not satisfy usage requirement, since marks could be affixed to goods themselves, and marks were used on products in purely descriptive manner, rather than as a source identifier. Lanham Trade–Mark Act, § 43(a)(1), 15 U.S.C.A. § 1125(a)(1).

23. Trade Regulation ⇐66.1

Use of unregistered mark on documents does not satisfy usage requirement of trademark infringement claim when the mark can be affixed to the goods themselves. Lanham Trade–Mark Act, § 43(a)(1), 15 U.S.C.A. § 1125(a)(1).

Alan M. Anderson, Fulbright & Jaworski L.L.P., of Minneapolis, MN, argued for plaintiffs-appellants. With him on the brief was Christopher K. Larus.

Warren E. Olsen, Fitzpatrick, Cella, Harper & Scinto, of Washington, DC, argued for defendant-cross appellant. With him on the brief were Brian L. Klock and Stephen E. Belisle.

Before NEWMAN, LOURIE, and CLEVENGER, Circuit Judges.

LOURIE, Circuit Judge.

Transclean Corporation, James P. Viken, Jon A. Lang, and Donald E. Johnson (collectively "Transclean") appeal from a judgment of the United States District Court for the District of Minnesota (1) reversing entry of a portion of a jury's damages award for infringement of Transclean's U.S. Patent 5,318,080, *Transclean Corp. v. Bridgewood Serv., Inc.*, No. 97–2298, slip op. at 28 (D.Minn. Jan. 8, 2001) ("*Damages Opinion*"); (2) denying its motion for enhanced damages under 35 U.S.C. § 284, *id.* at 66, as well as attorney fees under 35 U.S.C. § 285 and Minn.Stat. § 8.31, *Transclean Corp. v. Bridgewood Servs., Inc.*, 134 F.Supp.2d 1049, 1061 (D.Minn.2001) ("*Attorney Fees Opinion*"); and (3) granting summary judgment of noninfringement on its claim of trademark infringement, *Transclean Corp. v. Bridgewood Serv., Inc.*, 77 F.Supp.2d 1045, 1094–95 (D.Minn.1999) ("*Summary Judgment Opinion*"). Bridgewood cross-appeals from the court's grant of summary judgment that the '080 patent is not invalid for anticipation and that Bridgewood infringed claims 1–4 and 12. *Id.* at 1063, 1081, 1083. Bridgewood also cross-appeals from the court's denial of its motion for summary judgment of noninfringement of claim 13. *Id.* at 1087. For the reasons set forth below, we affirm-in-part and vacate-in-part.

BACKGROUND

Transclean is the assignee of the '080 patent, which is directed to an automatic transmission fluid changing apparatus. The fluid circulates from an automobile's automatic transmission case to a radiator and back via circulation lines. '080 patent at col. 1, ll. 6–12. The invention of the patent is designed to tap into a fluid circulation line and become part of the circulation system for the duration of the fluid changing procedure. *Id.* at col. 3, ll. 8–19. In that configuration, the invention collects used fluid as it circulates around and into the machine, while supplying new fluid into the circulation system. *Id.* Prior to the invention, such machines were not capable of matching the supply rate of new fluid to the outflow rate of used fluid. *Id.* at col. 2, ll. 56–68. As a result, one of two problems was likely to occur. First, if the supply rate was less than the outflow rate, the transmission could become starved of fluid, which could lead to excessive heating and

damage to the transmission. *Id.* Second, if the supply rate exceeded the outflow rate, a buildup of internal fluid pressure could stress and damage seals in the transmission. *Id.* The invention aimed to solve these problems by balancing the supply rate to the outflow rate. *Id.* at col. 3, ll. 8–19. Claim 1, the only independent claim, reads as follows:

> 1. In a fluid replacing apparatus for an automatic transmission an improvement having fluid circulation inlet and outlet ports comprising:
>
> a fluid receiver adapted to be connected to the fluid circulation output port on said automatic transmission;
>
> a source of fresh transmission fluid adapted to be connected to the fluid circulation inlet port on said automatic transmission so that fluid circulates therethrough; and
>
> *means* connected to said fluid receiver and said source of fresh fluid, *for equalizing the fluid flow into said fluid receiver and out of said source of fluid.*

Id. at col. 8, ll. 10–23 (emphases added).

As can be seen, the claims recite a "means . . . for equalizing the fluid flow" in the manner authorized by 35 U.S.C. § 112, ¶ 6. The specification discloses several structures corresponding to the claimed "means." According to one structure, the fluid receiver and source of fresh transmission fluid are segregated portions of the same tank, and the means for equalizing is a flexible diaphragm that defines the boundary dividing the tank into two segregated portions. *Id.* at figure 3. A structure with those characteristics is the subject of claim 13, which reads as follows:

> 13. The apparatus of claim 1 in which the means for equalizing the flow is comprised of means disposed intermediate the fluid receiver and source, said means *exhibiting resilient characteristics* for exerting a force, related to the pressure existing in the fluid circulation circuit of said transmission and said receiver, upon the fluid in said source.

Id. at col. 8, ll. 55–61 (emphasis added). Another structure corresponding to the means for equalizing in claim 1 is a pair of tanks, one for used fluid and one for fresh fluid charged by pressurized air. *Id.* at figs. 4,6.

Bridgewood is a competing distributor of transmission service equipment to automobile service businesses. Bridgewood's accused device is the embodiment described in its own U.S. Patent 5,522,474. Briefly, Bridgewood's device consists of a reservoir divided into two chambers by a free floating piston. '474 patent, abstract. The reservoir above the piston is initially filled with fresh fluid, and the reservoir below the piston is initially empty and compressed. *Id.* Extending from each chamber is a line for connection to an automobile's automatic transmission fluid circulation system at a point where a technician breaks the fluid circuit. *Id.* Thereafter, operation of the transmission pump sends used fluid into the bottom chamber, thereby forcing the piston to expel fresh fluid from the top chamber into the transmission's fluid circulation system. *Id.* When the technician can see fresh fluid being pumped into the bottom chamber, the procedure is halted, as the fluid has been essentially completely replaced, *id.*, even though not all of the used fluid could possibly be expelled, *Attorney Fees Opinion* at 1056.

Bridgewood is no longer in business, having sold all of its assets, including goodwill, to Century Manufacturing Company for a total of $7,744,000, which was $6,522,000 above and beyond the book value of Bridgewood's tangible net worth. Century subsequently took a license under the '080 patent from Transclean, agreeing to a royalty rate of nine percent.

Transclean sued Bridgewood for infringement of the '080 patent and its TOTAL FLUID EXCHANGE and TOTAL FLUID X CHANGE trademarks, as well as false advertising by Bridgewood's promotional claims that its device replaced "100%" or "every drop" of fluid. Before trial, both parties filed motions for partial summary judgment, Transclean seeking summary judgment on the issues of patent infringement and validity, and Bridgewood seeking summary judgment of noninfringement of claim 13 as well as Transclean's trademarks. The court granted all of those motions except that relating to claim 13. More specifically, the court granted summary judgment that the '080 patent was not anticipated by either U.S. Patent 3,513,941, issued to N.J. Becnel, or Japanese Patent 2–72299. *Summary Judgment Opinion* at 1081. Furthermore, the court granted Transclean's motion for summary judgment that Bridgewood infringed claims 1–4 and 12 of the '080 patent, after precluding Bridgewood from arguing noninfringement of those claims as a sanction for Bridgewood's failure to answer an interrogatory seeking its bases for arguing noninfringement. *Id.* at 1062–63. Finally, the court granted Bridgewood's motion that Bridgewood had not infringed Transclean's trademarks. *Id.* at 1094–95.

The case was then tried to a jury, which found that Bridgewood willfully infringed claim 13 and engaged in false advertising. The jury awarded Transclean three types of damages for the patent infringement. *Damages Opinion* at 3. The first was a reasonable royalty based on Bridgewood's sales of infringing devices; the second was additional damages for the infringement; and the third was a reasonable royalty based on Bridgewood's sale of its business. *Id.*

In a post-trial motion, Bridgewood sought to overturn the jury's damages awards. The court partly agreed and held that as a matter of law Transclean was not entitled to more than $1,874,500 for patent infringement. *Id.* at 65–66. Transclean also filed a post-trial motion seeking enhanced damages and attorney fees pursuant to 35 U.S.C. §§ 284 and 285 in light of the jury's finding of willful infringement, but the court denied both requests. *Id.* at 66. Additionally, Transclean filed a post-trial motion pursuant to Minnesota's private attorney general statute, Minn.Stat. § 8.31, seeking attorney fees it incurred in pursuing the false advertising claim, but the court denied that request as well. *Id.*

Transclean appeals and Bridgewood cross-appeals from the decisions of the district court. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

We review a district court's grant of summary judgment *de novo*, reapplying the same standard used by the district court. *Ethicon Endo–Surgery, Inc. v. U.S. Surgical Corp.*, 149 F.3d 1309, 1315, 47 USPQ2d 1272, 1275 (Fed.Cir.1998). Summary judgment is appropriate "if the pleadings, depositions, answers to interrogatories, and admissions on file, together with the affidavits, if any, show that there is no genuine issue as to any material fact and that the moving party is entitled to a judgment as a matter of law." Fed. R.Civ.P. 56(c). "The evidence of the nonmovant is to be believed, and all justifiable inferences are to be drawn in his favor." *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 255, 106 S.Ct. 2505, 91 L.Ed.2d 202 (1986). When both parties move for summary judgment, the court must evaluate each motion on its own merits, resolving all reasonable inferences against the party whose motion is under consideration. *McKay v. United States*, 199 F.3d 1376, 1380 (Fed.Cir.1999).

We review a district court's grant of judgment as a matter of law ("JMOL") *de novo*, reapplying the JMOL standard used by the district court. *Sextant Avionique, S.A. v. Analog Devices, Inc.*, 172 F.3d 817, 824, 49 USPQ2d 1865, 1869 (Fed.Cir.1999). JMOL is appropriate when "a party has been fully heard on an issue and there is no legally sufficient evidentiary basis for a reasonable jury to find for that party on that issue." Fed.R.Civ.P. 50(a)(1). To prevail, an appellant "must show that the jury's findings, presumed or express, are not supported by substantial evidence or, if they were, that the legal conclusion(s) implied from the jury's verdict cannot in law be supported by those findings." *Perkin–Elmer Corp. v. Computervision Corp.*, 732 F.2d 888, 893, 221 USPQ 669, 673 (Fed. Cir.1984) (citation omitted).

[1, 2] A determination that a patent is invalid as being anticipated under 35 U.S.C. § 102 requires a finding that "each and every limitation is found either expressly or inherently in a single prior art reference." *Celeritas Techs. Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1360, 47 USPQ2d 1516, 1522 (Fed.Cir.1998). To anticipate, the reference must also enable one of skill in the art to make and use the claimed invention. *In re Donohue*, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir.1985). Because a patent issued by the U.S. Patent and Trademark Office is presumed to be valid, 35 U.S.C. § 282 (1994), the evidentiary burden to show facts supporting a conclusion of invalidity is clear and convincing evidence, *WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1355, 51 USPQ2d 1385, 1396–97 (Fed.Cir. 1999).

[3–5] A determination of infringement requires a two-step analysis. "First, the court determines the scope and meaning of the patent claims asserted ... [Second,] the properly construed claims are compared to the allegedly infringing device." *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454, 46 USPQ2d 1169, 1172 (Fed. Cir.1998) (en banc) (citations omitted). Step one, claim construction, is an issue of law, *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 970–71, 34 USPQ2d 1321, 1322 (Fed.Cir.1995) (en banc), *aff'd*, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996), that we review *de novo*, *Cybor*, 138 F.3d at 1456, 46 USPQ2d at 1172 (Fed.Cir.1998). Step two, comparison of the claim to the accused device, requires a determination that every claim limitation or its equivalent be found in the accused device. *Warner–Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29, 117 S.Ct. 1040, 137 L.Ed.2d 146 (1997). Those determinations are questions of fact. *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353, 48 USPQ2d 1674, 1676 (Fed.Cir.1998).

[6, 7] The choice of methodology for calculating damages is within the discretion of the district court. *SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 926 F.2d 1161, 1164, 17 USPQ2d 1922, 1925 (Fed.Cir.1991). In any event, the patent owner bears the burden of proving by a preponderance of the evidence the quantum of damages, an issue of fact for which we review the jury's decision for substantial evidence. *Id.* at 1164 n. 2, 17 USPQ2d at 1925 n. 2.

[8] A decision to sanction a litigant pursuant to Fed.R.Civ.P. 37 is one that is not unique to patent law, *DH Tech., Inc. v. Synergystex Int'l, Inc.*, 154 F.3d 1333, 1343, 47 USPQ2d 1865, 1873 (Fed.Cir. 1998), and we therefore apply regional circuit law to that issue, *Midwest Indus., Inc. v. Karavan Trailers, Inc.*, 175 F.3d 1356, 1359, 50 USPQ2d 1672, 1675 (Fed.Cir. 1999) (en banc in relevant part). Because the Eighth Circuit, the pertinent regional circuit in this case, reviews the imposition of sanctions under Rule 37 for an abuse of discretion, *Givens v. A.H. Robins Co.*, 751

F.2d 261, 263 (8th Cir.1984), we will do the same.

On appeal Transclean raises a number of issues concerning damages and trademark infringement. First, Transclean argues that the court erred in disallowing the jury's award of a reasonable royalty on Bridgewood's proceeds from the sale of its business. Second, Transclean argues that the court abused its discretion by not awarding it enhanced damages and attorney fees for patent infringement under 35 U.S.C. §§ 284 and 285. Third, Transclean argues that the court erred in not awarding it attorney fees for pursuing the false advertising claim. Finally, Transclean argues that the court erred in granting summary judgment of noninfringement of its trademarks.

Bridgewood cross-appeals the court's judgments of patent validity and infringement. In particular, Bridgewood argues that the court erred in granting summary judgment that the '080 patent is not invalid for anticipation under 35 U.S.C. § 102. As to infringement, Bridgewood argues that the court abused its discretion when it estopped Bridgewood from contesting infringement of claims 1–4 and 12 as a discovery sanction and when it denied Bridgewood's motion for summary judgment of noninfringement of claim 13. We address each issue in turn.

A. *Patent Validity*

[9] Bridgewood asserts in its cross-appeal that the court erred when it granted summary judgment that neither the Becnel patent nor the Japanese patent anticipates the claims of the '080 patent. Although this is a cross-appealed issue, as is that on patent infringement, we deal with them first because they logically precede damages issues, which are the principally appealed issues. Bridgewood contends that the court misconstrued the phrase "means for equalizing the fluid flow" appearing in claim 1 by requiring that the fluid flow rate, rather than just the volume of fluid, be equalized. Based on its erroneously narrow construction of the claimed function, the court, according to Bridgewood, included extraneous structure in that corresponding to the "means for equalizing" limitation. Bridgewood asserts that the proper corresponding structure is a fresh fluid tank connected to a fresh fluid tube with a valve, a used fluid tank connected to a used fluid tube, and a source of pressurized air. Bridgewood contends that either the Becnel or Japanese patent discloses all of the minimum corresponding structure, and that the dependent claims recite well-known features that are also disclosed by the Becnel or Japanese patents.

Transclean responds that the court properly interpreted the term "flow" to mean a rate, not a volume, as the specification discloses that equalization of flow rates is the objective of the invention. Transclean further contends that the invention disclosed in the Becnel patent does not necessarily equalize flow rates, and that the Japanese patent discloses an apparatus that equalizes fluid weights, not flow rates.

We agree with Transclean that the claim phrase "equalizing the fluid flow" refers to a rate, not just a volume. To construe that phrase, we look to the specification for guidance, *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582, 39 USPQ2d 1573, 1577 (Fed.Cir.1996), and the specification clearly refers to the equalization of flow rates. For example, the patent describes problems that can occur in the prior art when the input flow rate of added fluid does not match the output flow rate of used fluid:

> [I]n the event fluid is allowed to drain *faster than the rate of addition* of fluid, the pump or torque converter in a

> transmission is likely to be starved and then will become excessively hot under which conditions a transmission will self-destruct if permitted to continue in operation. On the other hand, should excessive fluid be added to build up an internal pressure within the transmission, there is a strong likelihood that seals for shafts and/or valves, bearings, or the like or other internal components, within the transmission, may be irreparably damaged with a resulting failure of the transmission under subsequent operating conditions.

'080 patent at col. 2, ll. 56–68 (emphasis added). Furthermore, the "Summary of the Invention" states that the invention solves those problems:

> Briefly, my invention is comprised of a fluid receiver for used fluid, a source of supply of fresh fluid, and a means for coordinating the introduction of fresh fluid with the draining of used fluid. With this in mind, it then only remains necessary to separate the fluid flow in a line that is external from the transmission so that *the used fluid is drained into a suitable fluid container and the new fluid is introduced at the same rate that the used fluid exits.* This can be accomplished in a number of ways, some of which will be described in more detail below.

Id. at col. 3, ll. 8–17 (emphasis added). Other passages in the patent echo the same idea. *E.g., id.* at col. 5, ll. 51–53; col. 8, ll. 1–8. Because the specification is clear as to the meaning of the phrase "equalizing the fluid flow," and no other intrinsic evidence suggests a different meaning for the phrase, we affirm the district court's construction of that phrase to require equalization of flow rate.

[10, 11] As the parties agree, the phrase "means for equalizing fluid flow" is a means-plus-function limitation governed by 35 U.S.C. § 112, ¶ 6, and the recited function is "equalizing fluid flow." To anticipate a claim reciting a means-plus-function limitation, the anticipatory reference must disclose the recited function identically. *Cf. Wenger Mfg., Inc. v. Coating Mach. Sys., Inc.*, 239 F.3d 1225, 1238, 57 USPQ2d 1679, 1689 (Fed.Cir.2001) ("Literal infringement of a means-plus-function claim requires that the accused device have structure for performing the identical function recited in the claim."). In this case, neither the Becnel nor the Japanese patent contains such a disclosure.

The Becnel patent is described in the '080 patent as equalizing overall fluid volume, not flow rate. '080 patent at col. 1, l. 38—col. 2, l. 68. Bridgewood presented testimony from Becnel, the inventor, that his invention could be operated in such a manner as to equalize flow rates. However, as the district court found, that manner is not disclosed in the Becnel patent itself, nor is it inherent in the operation of Becnel's invention. *Summary Judgment Opinion* at 1081 ("Becnel was able to read the fluid gauges, and then manually adjust the flow of fresh fluid so as to equalize the fluid flows, but neither his declaration, nor [Bridgewood's patent expert's] opinion, offer any explanation as to how a person of ordinary skill would read the Becnel Patent specification, and recognize that this method of flow equalization is necessarily present in the embodiment disclosed in Fig. 5."). We conclude, as did the district court, that Bridgewood did not raise any genuine issue of material fact regarding anticipation of claim 1 by the Becnel patent. Accordingly, we affirm the court's conclusion that Transclean is entitled to summary judgment of non-anticipation as to the Becnel patent.

[12] The Japanese patent likewise discloses equalization of fluid amount, but not necessarily fluid flow rates. Broadly speaking, the Japanese patent describes

an "ATF [automatic transmission fluid] exchanger device," Jap. Pat. 2–72299, abstract (English translation), which, like the invention described in the '080 patent, comprises a supply of fresh fluid, a receptacle for used fluid, and hoses for connection to a transmission's fluid circulation system. *Id.* However, the Japanese apparatus also includes scales for measuring the weights of the fresh fluid supplied and used fluid removed, as well as a "detection means so that the difference between the amount of fluid drained and the amount of fluid supplied is maintained within an indicated range; and which automatically balances the amount of fluid drained and fluid supplied within an indicated range." Thus, the Japanese patent explicitly discloses that fluid weight is equalized, not necessarily fluid flow rate. Although it is possible that the detection means could under some circumstances (*e.g.*, if the response time for the feedback loop is sufficiently fast) effectively equalize the flow rates as well, it is also possible for that not to be the case. Because anticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation, *Cont'l Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268–69, 20 USPQ2d 1746, 1749 (Fed.Cir.1991) (emphasis added), the Japanese patent cannot inherently anticipate the claims of the '080 patent. We conclude, as did the district court, that Bridgewood did not raise any genuine issue of material fact regarding anticipation of claim 1 by the Japanese patent, and we therefore affirm the court's conclusion that Transclean is entitled to summary judgment of non-anticipation as to the Japanese patent. Thus, we affirm the court's conclusion that the claims of the '080 patent are not invalid under 35 U.S.C. § 102 as being anticipated by the Becnel or Japanese prior art patents.

B. *Patent Infringement*

[13] Bridgewood argues that the court abused its discretion when, as a discovery sanction, it precluded Bridgewood from asserting that it did not infringe claims 1–4 and 12, and when it denied Bridgewood's motion for summary judgment of noninfringement of claim 13. Regarding the first point, Bridgewood argues that the court impermissibly invoked an extreme discovery sanction without notice to Bridgewood, that Transclean was not prejudiced by Bridgewood's lack of response to Transclean's interrogatory, and that the court avoided its duty to construe the claim and relieved Transclean of its burden to prove infringement. Transclean responds that it was prejudiced by the lack of discovery and that the sanction was consistent with precedent.

We conclude that the district court acted within its discretion when it granted summary judgment of infringement as a discovery sanction. Because the imposition of a discovery sanction is not a matter substantially related to patent law, we apply the law of the regional circuit, in this case the Eighth Circuit. *See Midwest Indus.*, 175 F.3d at 1359, 50 USPQ2d at 1675. Although the entry of judgment is an extreme sanction in the Eighth Circuit (and elsewhere), *Givens*, 751 F.2d at 264, we are not convinced that the district court abused its discretion. Transclean legitimately sought to discover Bridgewood's grounds for its defense of noninfringement and was entitled to a reply to its interrogatory. When Bridgewood chose not to respond before the closing of discovery other than to voice its belief that the '080 patent was invalid and unenforceable, *Summary Judgment Opinion* at 1059–60, 1060–61, the court was within its discretion to impose a sanction. The court found clear prejudice to Transclean, as it was precluded from conducting discovery on the in-

fringement issues. *Id.* at 1063. To hold that the district court abused its discretion would be to disarm the court of its important power to police its proceedings to ensure transparency and predictability and to discourage mischievous conduct by litigants. It will be a rare case in which we take such an action. Moreover, even if a lesser sanction such as exclusion of evidence may have been more closely tailored to the misconduct, *see Givens*, 751 F.2d at 263 (characterizing evidence exclusion as the "normal sanction" for failure to comply with a discovery deadline), the practical result would have been the same. Transclean's motion for summary judgment of infringement presented evidence sufficient to show infringement, and, in light of Bridgewood's non-response, that evidence was uncontradicted. Accordingly, we affirm the district court's grant of summary judgment of infringement of claims 1–4 and 12 of the '080 patent.

[14] As for the second alleged abuse of discretion, denial of Bridgewood's motion for summary judgment of noninfringement of claim 13, Bridgewood argues that the court misconstrued the phrase "exhibiting resilient characteristics" to mean "returning to an original shape after being deformed" or "returning to its original position after being compressed." *Summary Judgment Opinion* at 1087. Bridgewood contends that initial deformation of shape is inherent in the meaning of the expression and cites technical dictionary definitions in support of that contention. Under the correct construction of that expression, according to Bridgewood, the free-floating piston in its device does not "exhibit[ ] resilient characteristics." Moreover, Bridgewood contends that prosecution history estoppel and the all-limitations rule bar Transclean from asserting infringement under the doctrine of equivalents for that claim limitation because claim 13, in which it appears, was added during prosecution, whereas the originally submitted claims did not contain that limitation, and because vitiation of the "exhibiting resilient characteristics" limitation would result. Transclean responds that claim 13 requires only that "said means exhibit[ ] resilient characteristics," not that the means itself be "resilient." Transclean also cites common dictionary definitions and expert testimony in support of its view that the term "resilient" does not require initial deformation. Moreover, Transclean contends that claim 13 itself was never narrowed during prosecution and that Bridgewood's prosecution history estoppel argument was not raised in the district court and has therefore been waived.

Because we affirm the judgment of infringement of claims 1–4 and 12, we need not review the court's ultimate conclusion regarding infringement of claim 13. Bridgewood has already been held to be an infringer, and infringement of another claim does not increase its liability. *See Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1220, 36 USPQ2d 1225, 1231 (Fed.Cir.1995). However, to put to rest any doubts regarding the proper construction of claim 13, because the patent has not been shown to be invalid and the issue has been fully ventilated by the parties, we will address that issue. We agree with Bridgewood that the court misconstrued the term "resilient." Dictionaries, both general and technical, define the adjective "resilient" or its noun form "resilience" as encompassing that which returns to its original shape following a deformation in shape. *See, e.g., McGraw–Hill Dictionary of Scientific and Technical Terms* 1693 (5th ed.1994) (defining the term "resilience" as the "[a]bility of a strained body, by virtue of high yield strength and low elastic modulus, to recover its size and form following deformation"); *American Heritage Dictionary* 1535 (3rd ed.1992) (defining the term "resilient" as "returning to an original shape or position, as after having been

compressed"). The dissent, as did the district court, focuses on the word "or" in the preceding definition to support its view that the term "resilient" encompasses the returning to a position alone, without any shape deformation. We do not think that the use of the word "or" in that definition can overcome the meaning attributed to the term "resilient" by the patent's disclosure of only a flexible diaphragm dividing a tank into two chambers. *See* '080 patent; fig. 3; col. 4, ll. 54–55 (depicting and describing "a flexible rubber-like diaphragm"). Furthermore, to the extent there is a difference between the common and technical meanings of the terms, the term "resilient" is used in the '080 patent in a technical context to describe a component of a mechanical apparatus, and a technical dictionary is therefore a better source to inform the meaning of the term to a skilled artisan in this case. Moreover, we do not share the dissent's view that the phrase "exhibiting resilient characteristics" describes a function in a means-plus-function limitation. On the contrary, the means-plus-function limitation further defined in claim 13 is the "means for equalizing the flow" previously set forth in claim 1. *Id.* at col. 8, ll. 20–23, ll. 55–61. According to the claim language, the only function performed by that "means" is "equalizing the flow." The phrase "exhibiting resilient characteristics" is not a second function performed by that "means"; rather, the phrase further defines characteristics of that "means." It is therefore, appropriate, indeed mandatory under 35 U.S.C. § 112, ¶ 6, to look to the corresponding structure in the specification to ascertain the meaning of the phrase. As already noted, that corresponding structure, "a flexible rubber-like diaphragm," '080 patent, col. 4, ll. 54–55, is "resilient" in the sense that it tends to return to its original shape, not just its original position. We therefore conclude that the phrase "exhibiting resilient characteristics" in the '080 patent requires initial shape deformation. Because the jury's finding of infringement of claim 13 was premised on a construction of that phrase at odds with ours, we vacate the judgment of infringement of claim 13.

C. *Patent Infringement Damages*

[15] The jury awarded three types of damages for patent infringement: (1) $934,618 as a reasonable royalty on Bridgewood's sales of infringing devices; (2) $1,874,500 as "additional damages ... necessary to adequately compensate for Bridgewood's infringement"; and (3) $2,708,225 as a reasonable royalty based upon Bridgewood's proceeds from the sale of its business to Century. *Damages Opinion* at 3. The court reversed the third award, holding that Transclean was not entitled to such an award as a matter of law. *Id.* at 65. As to the first and second, the court granted Bridgewood's motion for a new trial or remittitur in the amount of $1,874,500, the highest amount, based on the evidence, that the jury could have properly awarded for patent infringement. *Id.* at 61, 66. Transclean apparently accepted the remittitur.

Transclean appeals from the court's decision concerning the third award only. Transclean cites *Minco, Inc. v. Combustion Eng'g, Inc.*, 95 F.3d 1109, 40 USPQ2d 1001 (Fed.Cir.1996) in support of its argument that, because Bridgewood's sole source of revenue was an infringing product and Bridgewood generated $6,500,000 in goodwill from the sale of its business to Century, Transclean is entitled to recover the value of that goodwill. Transclean asserts that to allow Bridgewood to retain that windfall would create an incentive for others to infringe a patent and then sell their businesses.

Bridgewood responds that this case is distinguishable from *Minco* because that case involved lost profits, not a reasonable

royalty, and a reasonable royalty must be based on sales of infringing articles. Bridgewood contends that payment for goodwill is not the sale of infringing goods, was attributable to many factors other than the technology of its fluid changing machines, and that Transclean did not prove a nexus between the patent infringement and the value of the goodwill.

We agree with Bridgewood that *Minco* does not control this case. As indicated, it was a lost profits case, not one based on a reasonable royalty. Although *Minco* acknowledged that "fashioning an adequate damages award depends on the unique economic circumstances of each case," 95 F.3d at 1118, 40 USPQ2d at 1007, we held that the patent owner in that case could not recover damages based on the infringer's sale of its business. *Id.* at 1121. More specifically, the patent owner sought lost profits calculated as the difference between the sales price of the infringer's business and its expert's valuation of the business without the infringing devices. *Id.* at 1120. The patent owner asserted that the purchaser would have purchased its business instead of the infringer's, had it not been for the infringement, *id.*, and the excess sales price thus constituted part of the patent owner's lost profits. The district court did not accept that assertion, and we affirmed that decision. *Id.* at 1121. Furthermore, we explained that any award based on the infringer's sale of its business would be duplicative of the reasonable royalty the infringer had already received based on the infringer's sales of infringing goods. *Id.* ("The district court's reasonable royalty award already compensates [the patent owner] for any goodwill [the infringer] garnered by infringement."). Transclean's citation of *Minco* as controlling this case is thus unsound; it is an example of the unhelpful advocacy that is at times made to this court, in which counsel cites general language from a prior case, rather than its holding. In fact, the holding of *Minco* supports Bridgewood's position, not Transclean's.

We must analyze Transclean's claim for a percentage of Bridgewood's business sale proceeds as it was asserted, as a claim for a reasonable royalty, not for lost profits. Reasonable royalty damages for patent infringement arise from the fact of infringement, and the portion of the sales price consisting of intangible goodwill is not the sale of infringing goods. It is partial compensation for the sale of a business. Whether or not proceeds from the sale of a business including tangible assets such as infringing inventory would be compensable as a remedy for patent infringement we are not in a position to say; that case is not before us. What is clear is that the portion of a sales price consisting of goodwill, *i.e.*, compensation in excess of tangible assets, is not sales of infringing goods that can form the base for determination of a reasonable royalty. No such precedent exists, nor are we prepared to distort the statute to set one.

In addition, as a matter of proof, Transclean has not established the amount, if any, of a reasonable royalty on Bridgewood's sale of its business it is entitled to recover. Transclean had the burden of proving the amount of reasonable royalty damages it is entitled to recover. *Id.* The most relevant inquiry in that respect would seem to be the amount of the business's value that is attributable to the patent infringement. Transclean offered expert testimony that the entire goodwill above and beyond the value of Bridgewood's tangible assets was attributable to patent infringement because Bridgewood was a single product company and that product infringed Transclean's patent. *Damages Opinion* at 29–30. However, the district court disagreed, concluding that the opinion testimony was conclusory and belied by Bridgewood's arguments

that Bridgewood's goodwill was attributable to other factors (*e.g.*, customer lists, brand identity, product quality, and pricing). *Id.* at 30–31. We perceive no error in the district court's analysis or conclusion. Moreover, to the extent that Transclean argues that the goodwill was ultimately attributable to Bridgewood's sales of infringing machines, any award of reasonable royalty damages based on goodwill transferred when the business was sold would be a double recovery, as Transclean has already been awarded damages that fully compensate it for Bridgewood's past sales. *See Minco*, 95 F.3d at 1121, 40 USPQ2d at 1010 ("The district court's reasonable royalty award already compensates [the patent owner] for any goodwill [the infringer] garnered by infringement."). To the extent that the extra recovery Transclean seeks would be duplicative, we see no merit to Transclean's argument that Bridgewood is retaining a windfall that would create an incentive for infringers to sell infringing businesses with impunity.

For the reasons stated above, we conclude that the court did not err when it ruled that, as a matter of law, Transclean was not entitled to a reasonable royalty on proceeds from Bridgewood's sale of its business.

D. *Enhanced Damages*

[16] The jury found that Bridgewood's infringement was willful. Transclean argued to the jury that it made Bridgewood aware of the '080 patent, but that Bridgewood did not obtain an opinion of counsel and did not abate its manufacture or sale of the infringing machines. Bridgewood argued that the fact that it obtained its own patent on an automatic transmission fluid changing machine demonstrated a good faith belief that it was not an infringer. Bridgewood argued that when it received advice from its patent attorney concerning the patentability of its invention over the '080 patent, it received an implicit opinion of noninfringement. Although the jury agreed with Transclean that Bridgewood had willfully infringed the '080 patent, the court, after applying the factors set forth in *Read Corp. v. Portec, Inc.*, 970 F.2d, 816, 826–27, 23 USPQ2d 1426, 1435–36 (Fed.Cir.1992) (listing nine factors), declined to enhance the patent infringement damages. *Damages Opinion* at 13–22.

Transclean contends that the court abused its discretion by not enhancing the damages in light of the jury's finding of willfulness. Transclean also asserts that the court erroneously assumed that the only way it could enhance the damages was by trebling them, misunderstanding that an enhancement of less than trebling was a permissible option. Bridgewood responds that a finding of willful infringement does not mandate enhancement of damages, that the court did not misunderstand the law on enhancement, and that the court properly considered the *Read* factors.

[17] We agree with Bridgewood that the court acted within its discretion in not enhancing the damages award. Enhancement of damages under 35 U.S.C. § 284 involves the fact-finder determining that the infringer engaged in culpable conduct and the court exercising its discretion to determine whether and to what extent to enhance the damages. *Jurgens v. CBK, Ltd.*, 80 F.3d 1566, 1570, 38 USPQ2d 1397, 1399 (Fed.Cir.1996). The jury's finding of willfulness satisfies the first step, *see id.*, and is also one of the factors the court assesses in performing the second step, *see Read*, 970 F.2d at 827, 23 USPQ2d at 1435. However, there are other factors relevant to the second step. *See id.* (listing as factors: (1) deliberate copying; (2) infringer's investigation and good-faith belief of invalidity or non-infringement; (3) litigation conduct; (4) infringer's size and finan-

cial condition; (5) closeness of the case; (6) duration of the misconduct; (7) remedial action by the infringer; (8) infringer's motivation for harm; and (9) concealment). A finding of willful infringement "*authorizes* but does not *mandate* an award or increased damages." *Modine Mfg. Co. v. Allen Group, Inc.*, 917 F.2d 538, 543, 16 USPQ2d 1622, 1625 (Fed.Cir.1990). In this case, the court considered the pertinent *Read* factors carefully, *Damages Opinion* at 13–22, and although we may or may not have reached a different conclusion if we had been in the district court's shoes, we wear our own shoes. We review the court's analysis for an abuse of discretion, and we are satisfied that such an abuse did not occur.

We also agree with Transclean that the court did not erroneously assume that its only options were to treble the patent infringement damages or not enhance the damages at all. The court's opinion states, "In exercising our discretion to enhance damages, however, we are limited 'to a trebling of the basic damage award.' " *Damages Opinion* at 10 (quoting *Signtech USA, Ltd. v. Vutek, Inc.*, 174 F.3d 1352, 1358–59, 50 USPQ2d 1372, 1376 (Fed.Cir. 1999)). We read that statement, as it was intended in *Signtech*, to simply recognize the upper range of the possible enhancement. *See Signtech*, 174 F.3d at 1358–59, 50 USPQ2d at 1376 ("[T]he district court enjoys discretion to choose whether to award enhanced damages to the claimant *and in what amount.* This discretion, however is limited to a trebling of the basic damage award.") (citations omitted) (emphasis added). Elsewhere in the same opinion, the court makes statements recognizing that a range of enhancement is possible. *See Damages Opinion* at 8 (" '[T]he court determines, exercising its sound discretion, whether, *and to what extent*, to increase the damages award . . .' ") (quoting *Jurgens*, 80 F.3d at 1570, 38 USPQ2d at 1399) (emphasis added); *Damages Opinion* at 21 (" 'The paramount determination in deciding to grant enhancement *and the amount thereof* is . . .' ") (quoting *Read*, 970 F.2d, at 826, 23 USPQ2d at 1435) (emphasis added). *See also Modine*, 917 F.2d at 543 n. 3, 16 USPQ2d at 1625 n. 3 ("[T]he fact that the court's opinion focuses upon treble damages does not necessarily mean that the judge failed to *consider* lesser multiples of damages.").

E. *Attorney Fees*

After the trial, Transclean filed a motion for attorney fees, and the court granted that motion in part, awarding Transclean its attorney fees arising from arguing two issues. First, pursuant to 35 U.S.C. § 285, the court awarded Transclean attorney fees for defense of a charge of inequitable conduct asserted by Bridgewood. *Damages Opinion* at 27. The court's opinion does not address attorney fees under 35 U.S.C. § 285 except in relation to the inequitable conduct issue. Second, pursuant to Minnesota's private attorney general statute, Minn.Stat. § 8.31, the court awarded Transclean attorney fees for its successful claim that Bridgewood engaged in false advertising by promoting its transmission fluid changing machine as replacing "100%" or "every drop" of transmission fluid. *Id.* However, the court later revoked that award for two reasons: Transclean had unclean hands by promoting its own service as a "total" fluid exchange, and Transclean did not object to Century's use of the same advertisements after Century had purchased Bridgewood and taken a license to the '080 patent from Transclean.

Transclean now argues that the court abused its discretion by not awarding Transclean attorney fees under 35 U.S.C. § 285 for its entire patent infringement claim when the jury determined that Bridgewood's infringement was willful and

by not stating its reasons for declining to award attorney fees apart from those related to inequitable conduct. Transclean further argues that the court abused its discretion by not ultimately awarding attorney fees under Minn.Stat. § 8.31 for its false advertising claim. Bridgewood responds that a finding of willful infringement does not mandate a determination that a case is exceptional, as that term is used in 35 U.S.C. § 285, and that not every exceptional case is deserving of an award of attorney fees. Bridgewood further responds that the court set forth legitimate reasons for not awarding attorney fees for the false advertising claim and thus acted within its discretion.

[18, 19] With regard to attorney fees for patent infringement, we agree with Bridgewood. Transclean is correct in stating the general rule that the district court must normally explain why it decides that a case is not exceptional under 35 U.S.C. § 285 when a factual finding of willful infringement has been established and, if exceptional, why it decides not to award attorney fees, *S.C. Johnson & Son, Inc. v. Carter-Wallace, Inc.*, 781 F.2d 198, 201, 228 USPQ 367, 369 (Fed.Cir.1986). However, we have recognized an exception to that general rule in cases where the record adequately sets forth grounds for affirming the district court's actions. *Carroll Touch, Inc. v. Electro Mech. Sys. Inc.*, 15 F.3d 1573, 1584, 27 USPQ2d 1836, 1845 (Fed.Cir.1993) (citing *Consol. Al. Corp. v. Foseco Int'l, Ltd.*, 910 F.2d 804, 814, 15 USPQ2d 1481, 1488–89 (Fed.Cir.1990)). In this case, the court's careful analysis of the *Read* factors regarding enhancement of damages suffices as grounds for affirming the court's implicit conclusion that the infringement case was not exceptional within the meaning of 35 U.S.C. § 285.

[20, 21] With regard to attorney fees for false advertising, we agree with Bridgewood. Transclean's claim for attorney fees arising from the false advertising cause of action was based on Minn.Stat. § 8.31. The purpose of that statute is to encourage private parties to police unlawful trade practices affecting the public interest. *Ly v. Nystrom*, 615 N.W.2d 302, 313–14 (Minn.2000). The court determined that, while Transclean's cause of action against Bridgewood for false advertising was on its face one that qualified for attorney fees under the statute, *Attorney Fees Opinion* at 11, Transclean's own use of advertising that was arguably equivalent in falsity and Transclean's tolerance of Century's use of the same advertising when it licensed Transclean's patent erased any public benefit accruing from the successful action against Bridgewood, *id.* at 12–14. The district court's reasoning is sound, and we discern no abuse of discretion in its decision not to award Transclean attorney fees for its false advertising claim.

F. *Trademark Infringement*

[22] Transclean brought a cause of action for trademark infringement, asserting that Bridgewood infringed Transclean's TOTAL FLUID EXCHANGE and TOTAL FLUID X-CHANGE unregistered trademarks under section 43(a) of the Lanham Act, 15 U.S.C. § 1125(a)(1), and Minnesota law. The court granted Bridgewood's motion for summary judgment of noninfringement on the ground that there was no genuine issue of material fact relating to Transclean's adequate usage of the marks in commerce. *Summary Judgment Opinion* at 1094–95. Transclean argues that a genuine issue of material fact regarding that issue was raised by an affidavit from James P. Viken, Transclean's CEO and inventor on the '080 patent, stating that Transclean had used the marks on its products and documents since 1994. *Id.* at 1093–94. Bridgewood responds that the affidavit is conclusory and

does not designate specific facts concerning the marks' usage.

[23] We agree with Bridgewood that Transclean failed to raise a genuine issue of material fact as to nondescriptive usage of the mark on the goods. We apply Eighth Circuit law to this issue, and the Eighth Circuit has recognized the universal requirement for actual usage of the mark in commerce, *First Bank v. First Bank Sys., Inc.*, 84 F.3d 1040, 1044 (8th Cir.1996). Use of the mark on documents does not satisfy the usage requirement when the mark can be affixed to the goods themselves, *Elec. Communications, Inc. v. Elec. Components for Industry Co.*, 443 F.2d 487, 492 (8th Cir.1971), as is the case here, *Summary Judgment Opinion* at 1094. Furthermore, the usage of the marks must be as a source identifier rather than as a description of the goods' qualities. *First Bank*, 84 F.3d at 1044. In this case, the Viken affidavit is deficient in two ways, even if assumed to be accurate. First, the reference to documents is irrelevant, *Elec. Communications*, 443 F.2d at 492–93. Second, on its face, the affidavit does not purport to show that the use was as a source identifier. Indeed, the record evidence shows that the marks were used in a purely descriptive manner, *e.g.*, "TFX TOTAL FLUID EXCHANGE SYSTEM FOR AUTOMATIC TRANSMISSIONS by Transclean Corp." Accordingly, the court did not err when it concluded that the Viken affidavit failed to raise a genuine issue of material fact regarding usage of the Transclean's marks, and we affirm the court's grant of summary judgment in favor of Bridgewood on the trademark claims.

CONCLUSION

We commend the district court for its thorough and competent handling of a complex case involving a large number of difficult issues. We affirm all aspects of the court's decision except one. The court did not err in granting summary judgment that the '080 patent is not anticipated by either the Becnel or Japanese prior art patents. Nor did the court err in granting summary judgment that Bridgewood did not infringe Transclean's trademarks, or in granting Bridgewood's post-trial motion for reversal of the jury's award of damages based on a reasonable royalty of Bridgewood's sale of its business. Furthermore, the court did not abuse its discretion in entering a judgment of infringement of claims 1–4 and 12 as a discovery sanction against Bridgewood. Nor did the court abuse its discretion when it declined to award Transclean enhanced damages and attorney fees under the patent statute or Minnesota law. However, the court did err when it construed the phrase "exhibiting resilient characteristics" in claim 13 of the '080 patent, and we therefore vacate the jury's determination, based on the court's erroneous claim construction, that Bridgewood infringed claim 13. Accordingly, we

AFFIRM–IN–PART and *VACATE–IN–PART.*

CLEVENGER, Circuit Judge, dissenting in part.

I agree with the majority's resolution of the validity, damages, and attorney fees issues as well as its determination that the district court did not abuse its discretion in precluding Bridgewood from asserting noninfringement of claims 1–4 and 12 as a sanction for various discovery abuses. Furthermore, I agree with the majority that the district court properly granted summary judgment to Bridgewood on Transclean's trademark infringement claim. However, in my view the majority's construction of the term "resilient" in claim 13 is unduly narrow and departs from the term's ordinary meaning. There-

fore, I respectfully dissent from that portion of the majority's opinion vacating the district court's claim construction and the jury's finding of infringement as to that claim.

This case asks us to decide the meaning of the word "resilient." That word is not defined in the specification. Indeed, "resilient" appears in the patent exactly once-in claim 13:

> The apparatus of claim 1 in which the means for equalizing the flow is comprised of means disposed intermediate the fluid receiver and source, said means *exhibiting resilient characteristics* for exerting a force, related to the pressure existing in the fluid circulation circuit of said transmission and said receiver, upon the fluid in said source.

U.S. Patent No. 5,318,080, col. 8, lines 55–61 (emphasis added). Because the patentee has not chosen to be his own lexicographer in this instance, "resilient" should carry its ordinary meaning in the art. Transclean asserts that "resilient" encompasses the ability to return to an original shape *or* position after being compressed, while Bridgewood argues that a resilient means must be capable of returning to an original shape *and* position after being compressed-in other words, that it must be inherently elastic.

To help us divine the meaning of "resilient," Transclean has provided dictionary definitions of "resilient" as well as expert testimony regarding what one of skill in the art would understand the term to mean. In contrast, Bridgewood proffers definitions of "resilience" from technical dictionaries. The district court properly rejected Bridgwood's definitions of "resilience" and adopted instead the ordinary meaning of the actual claim term, resil*ient*. The majority, based on the supposed superiority of technical dictionaries over ordinary dictionaries, prefers Bridgewood's definition.

The district court gave the word "resilient" its ordinary dictionary meaning, possessing "the capability of 'returning to an original shape *or position*, as after having been compressed.' " *Transclean Corp. v. Bridgewood Services, Inc.*, 77 F.Supp.2d 1045, 1087 (D.Minn.1999) (quoting *American Heritage Dictionary* 1535 (3d ed.1992) (emphasis added)). In other words, the broad term "resilient characteristics" can include a variety of different properties such as the ability to return to an original position after being exposed to a force, or the ability to return to an original shape after having been deformed. This meaning is in accord with the definition found in other common dictionaries. *See, e.g., Websters Third New International Dictionary (unabridged)* 1932 (defining resilient as "returning freely to a previous position, shape *or* condition: as a: moving swiftly back . . . b: capable of withstanding shock without permanent deformation or rupture . . . c: SPRINGY . . . ." (first emphasis added)); *Oxford English Dictionary* 714 (2d Ed.1989) (defining resilient as "1. Returning to the original position; springing back, recoiling, etc." and "2. Resuming the original shape or position after being bent, compressed, or stretched"); *Random House Webster's Unabridged Dictionary* 1638 (2d ed.1993) (defining resilient as "1. springing back; rebounding" and "2. returning to the original form *or* position after being bent, compressed, or stretched") (emphasis added). This meaning is in accord with the expert testimony proffered by Transclean, which explained that the patent uses the term resilient to mean "returning to the, some earlier position . . . or shape."

To support its proposed definition, Bridgewood cites various technical dictionaries that, supposedly, define " 'resilient' or 'resilience.' " A closer examination of these sources reveals, however, that the technical definitions provided by Bridge-

wood in fact relate the definition of "resilience" and not "resilient." And, unlike "resilient," "resilience" generally refers to the stored energy of a strained-and typically elastic-material. For example, *Van Nostrand's Scientific Encyclopedia* 2673 (8th ed.1995) defines resilience as follows: "resilience of a body measures the extent to which energy may be stored in it by elastic deformation." The *Dictionary of Mechanical Engineering* 314 (4th ed.1996) defines resilience as "[t]he stored energy of a strained or elastic material, such as in a compressed spring or in rubber dampers, which have inherent damping properties." *See also Chambers Dictionary of Science and Technology* 980 (1999) (defining resilience as the "[s]tored energy of a strained material, or the work done per unit volume of an elastic material by a bending moment, force, torque or shear force, in producing strain").

The majority chooses to rely upon Bridgewood's proffered definitions of "resilience" rather than the ordinary meaning of the actual claim term, "resilient," for two reasons. First, the majority finds that technical dictionaries are generally superior to common dictionaries. While dicta in *Bell Atlantic Network Services, Inc. v. Covad Communications Group, Inc.*, 262 F.3d 1258, 1267, 59 USPQ2d 1865, 1870 (Fed.Cir.2001), states the view that technical dictionaries are preferred to common dictionaries, neither that case nor the case upon which it relied, *Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 45 USPQ2d 1429 (Fed.Cir.1998), involved a conflict between a common dictionary definition and that found in a scientific treatise-and neither does this case. The technical definitions are simply inapt because they define the wrong word-resilience instead of resilient. Indeed, the "common dictionaries" rejected by the majority are the only sources before the court that define *both* resilient and resilience, and notably, they define resilience in the same way as the supposedly superior technical dictionaries. For example, *Webster's Third New International Dictionary* 1932 (1993) defines resilience as follows:

> 1a: an act of springing back: REBOUND, RECOIL, ELASTICITY b: capability of a strained body to recover its size and shape after deformation, esp. when the strain is caused by compressive stresses-called also *elastic resilience* 2: *the recoverable potential energy of an elastic solid body or structure due to its having been subjected to stress not exceeding the elastic limit.*

(Second emphasis added.) While it may often be preferable to look to a technical dictionary or treatise to provide the technical definition of a term as understood by practitioners of a particular art, I think that preference must fade when the technical dictionary does not provide a definition of the precise term used in the claim language. Therefore, I would hold that the trial court properly adopted the common dictionary definition of "resilient" as proffered by Transclean.

The majority shores up its view of the correct meaning for "resilient" by holding that the phrase "exhibiting resilient characteristics for exerting a force" does not describe part of the function of the "means for equalizing the flow" limitation. I disagree with that holding, for it is clear to me that the "exhibiting resilient characteristics" phrase does define function. If I am correct on this point, then of course it is impermissible to define the function by reference to structure disclosed in the written description. Function must be defined by reference to ordinary principles of claim interpretation, before proceeding to determine corresponding structure. *See Kemco Sales, Inc. v. Control Papers Co.*, 208 F.3d 1352, 1361, 54 USPQ2d 1308, 1313 (Fed.Cir.2000). The majority does not disagree with me on this point: if the phrase in question defines function, then

resort to the specification to find structure to define the function is simply wrong, and ordinary tools of claim interpretation apply.

Instead, the majority holds that the phrase in question is actually part of the means for equalizing the flow, and that resort to the specification is required to find the structure corresponding to the means limitation. Thus, from the specification the majority fetches the flexible rubber-like diaphragm, and thereupon concludes that "exhibiting resilient characteristics" must require initial shape deformation because that is the characteristic of the diaphragm.

The majority's rationale is self-destructive. If the diaphragm is indeed the structure that corresponds to the "means for equalizing the flow" limitation-as both parties and all the judges on the case agree-then the majority must come to grips with the stark fact that the jury found that the piston structure in Bridgewood's device is structurally equivalent, for § 112 ¶ 6 infringement purposes, to the diaphragm disclosed in Figure 3. Indeed, the case was submitted to the jury precisely to resolve disputed issues of fact on the structural equivalence of the accused piston and the diaphragm structure. No question has been raised that substantial evidence does not support the jury's verdict. Consequently, if, as the majority holds, "exhibiting resilient characteristics for exerting a force" must be understood as merely "further defin[ing] the structure of [the] means," *ante* at 1375, there is no possible basis for disturbing the jury's verdict of infringement.

In short, the majority is wrong on any interpretation of the disputed phrase. If the phrase describes function, it must be interpreted by ordinary interpretative canons, as did the district court. If the phrase is to be interpreted as part of the means limitation, as the majority holds, then the jury verdict of infringement must stand. Either way, the jury verdict of infringement cannot properly be upset, and I respectfully dissent from the majority on this point.